```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:10:23 ON 14 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 14 Jun 2006  VOL 144 ISS 25
FILE LAST UPDATED: 13 Jun 2006  (20060613/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d l61 all hitstr tot

L61  ANSWER 1 OF 26  HCAPLUS  COPYRIGHT 2006 ACS on STN
AN   2005:1240947  HCAPLUS
DN   144:11582
ED   Entered STN:  24 Nov 2005
TI   Process for the preparation of polymorphic crystalline forms of
     nateglinide ammonium salt
IN   Wizel, Shlomit; Frenkel, Gustavo; Gome, Boaz
PA   Teva Pharmaceutical Industries Ltd., Israel; Teva
     Pharmaceuticals Usa, Inc.
SO   PCT Int. Appl., 25 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07C0231-24
     ICS  C07C0233-63; A61K0031-16; A61P0003-00
CC   63-6 (Pharmaceuticals)
     Section cross-reference(s): 34, 75
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     --------------      ----   --------    --------------------   --------
PI   WO 2005110972        A1    20051124    WO 2005-US16343        20050509
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
             NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
             SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
             ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
```

US 2006004102 A1 20060105 US 2005-126050 20050509
EP 1656339 A1 20060517 EP 2005-748381 20050509
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU
PRAI US 2004-569047P P 20040507
WO 2005-US16343 W 20050509

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005110972	ICM	C07C0231-24
	ICS	C07C0233-63; A61K0031-16; A61P0003-00
	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	ECLA	C07C231/24; C07C233/63
US 2006004102	IPCI	A61K0031-198 [I,A]; A61K0031-185 [I,C*]
	NCL	514/563.000
EP 1656339	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	ECLA	C07C231/24; C07C233/63

AB Anti-hyperglycemic polymorphic **crystalline** forms of **nateglinide** ammonium salt are prepared

ST **nateglinide** ammonium salt polymorphic **cryst** form

IT Bicarbonates
Carbonates, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(Group IA and IIA metal, bases; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Alkali metal hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Alkali metal hydrides
Alkaline earth hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(bases; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT **Crystallization**
Neutralization
(in a process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(in a process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Diabetes mellitus
(non-insulin-dependent; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for the treatment of)

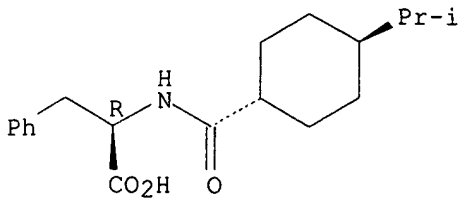
IT **Polymorphism (crystal)**
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Hyperglycemia
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for the treatment of)

IT Antidiabetic agents
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for use as)

IT Drug delivery systems
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for use in)
IT 1344-28-1D, Alumina, basic
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
IT 67-56-1, Methanol, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
IT **594837-89-5P**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
IT 1336-21-6, Ammonium hydroxide 7664-41-7, Ammonia, reactions **105816-04-4, Nateglinide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co Inc; EP 1334963 A 2003 HCAPLUS
(2) Ajinomoto Co Inc; EP 1334964 A 2003 HCAPLUS
(3) Ajinomoto Co Inc; EP 1496048 A 2005 HCAPLUS
(4) Fre; WO 2004067496 A 2004 HCAPLUS
(5) Koguchi, Y; US 5463116 A 1995 HCAPLUS
(6) Koguchi, Y; WO 03087039 A1 2003 HCAPLUS
(7) Kumashiro, I; US 4816484 A 1989 HCAPLUS
(8) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCAPLUS
(9) Shah, V; WO 03022251 A 2003 HCAPLUS
(10) Sutton, P; WO 03076393 A 2003 HCAPLUS
(11) Threlfall; ANALYST 1995, V120, P2435 HCAPLUS
(12) Yaha; WO 2004009532 A 2004 HCAPLUS
IT **594837-89-5P**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
RN 594837-89-5 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, ammonium salt (9CI) (CA INDEX NAME)

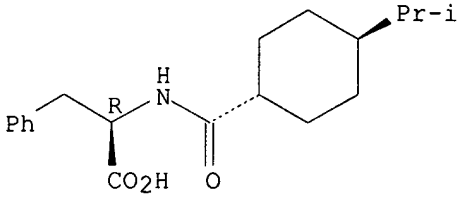
Absolute stereochemistry. Rotation (-).



●x NH_3

IT **105816-04-4, Nateglinide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:59980 HCAPLUS
DN 142:141289
ED Entered STN: 21 Jan 2005
TI **Crystalline** form of **nateglinide**
IN Frenkel, Gustavo; **Gome**, **Boaz**; Wizel, Shlomit
PA Israel
SO U.S. Pat. Appl. Publ., 91 pp., Cont.-in-part of U.S. Ser. No. 622,905.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K0031-198
ICS C07C0233-29
INCL 514563000; 562450000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, **75**
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005014836	A1	20050120	US 2003-746697	20031224 <--
US 2004181089	A1	20040916	US 2003-622905	20030718 <--
CA 2513753	AA	20040812	CA 2004-2513753	20040113 <--
WO 2004067496	A1	20040812	WO 2004-US839	20040113 <--
WO 2004067496	C2	20041209		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,

```
            CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
            LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
     EP 1511717          A1    20050309    EP 2004-701826        20040113 <--
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI US 2003-442109P      P     20030123
     US 2003-449791P      P     20030224
     US 2003-479016P      P     20030616
     US 2003-622905       A2    20030718  <--
     US 2002-396904P      P     20020718  <--
     US 2002-413622P      P     20020925  <--
     US 2002-414199P      P     20020926  <--
     US 2002-423750P      P     20021105  <--
     US 2002-432093P      P     20021210  <--
     US 2002-432962P      P     20021212  <--
     WO 2003-US22375      A     20030718
     US 2003-693166       A     20031023
     US 2003-746697       A     20031224
     WO 2004-US839        W     20040113  <--
CLASS
 PATENT NO.      CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------  -----  ----------------------------------------------
 US 2005014836   ICM    A61K0031-198
                 ICS    C07C0233-29
                 INCL   514563000; 562450000
                 IPCI   A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*];
                        C07C0233-29 [ICS,7]; C07C0233-00 [ICS,7,C*]
                 IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                        [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*];
                        C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02
                        [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*];
                        C07C0233-63 [I,A]
                 NCL    514/563.000
                 ECLA   A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02;
                        C07C231/24; C07C233/63
 US 2004181089   IPCI   C07C0233-30 [ICM,7]; C07C0233-00 [ICM,7,C*]
                 IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                        [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*];
                        C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02
                        [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*];
                        C07C0233-63 [I,A]
                 NCL    562/450.000
                 ECLA   A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02;
                        C07C231/24; C07C233/63
 CA 2513753      IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                        A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63
                        [ICS,7]; C07C0233-00 [ICS,7,C*]
                 IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61P0003-00
                        [I,A]; A61P0003-00 [I,C*]; C07C0231-00 [I,C*];
                        C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63
                        [I,A]
 WO 2004067496   IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                        C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];
                        A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
                 ECLA   C07C231/24; C07C233/63
 EP 1511717      IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                        C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];
```

A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
IPCR C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]

AB **Crystalline** forms of **nateglinide** and processes for their preparation, as well as pharmaceutical formulations containing them and methods of administration are provided. A process for preparing **crystalline** form of **nateglinide** comprises the steps of(a) preparing a solution of **nateglinide** in Et acetate, (b) seeding the solution with **nateglinide crystals**, and (c) recovering the **crystalline** form as a precipitate The **nateglinide** obtained is more than about 99% pure. For example, **nateglinide** (5 g) was dissolved in acetonitrile, acetone, or Et acetate at about 55° in over about 15 min until a clear solution was obtained. The solvent was removed to dryness by evaporation at about 55°/20 to 30 mmHg to give dry **nateglinide crystalline** Form B. Also, **nateglinide** Form Z was prepared by treating 7.73 g of D-phenylalanine (PheOH) with 185 mL (3.5 equiv) of 3.5% NaOH at room temperature to afford a clear solution of the corresponding Na-salt. A solution of neat trans-4-isopropylcyclohexanecarboxyl chloride (IPCHAC, 9.02 g, 1.01 equiv) was added to the solution of Phe-OH obtained above, over 3 min, while stirring at room temperature The rest of the IPCHAC in the funnel was washed with toluene (1 mL) and added. The resulting mixture was stirred for 1 h, and was treated with 10% HCl (32 mL) to adjust the pH to 3, while stirring. The mixture was stirred for 1 h, and filtered. The solid was washed with water (200 mL) and sucked well to afford 33.3 g of the moist product, which lost weight after drying at 78°/2.2 mbar (Assay 98.4%, purity >99% , yield 86%).

ST **nateglinide crystal** form prepn polymorphism dosage form

IT Hydrocarbons, processes
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(C5-12; preparation of **crystalline** form of **nateglinide** for dosage forms)

IT Solvents
(antisolvents; preparation of **crystalline** form of **nateglinide** for dosage forms)

IT **Crystal morphology**
Crystallization
Drug delivery systems
Polymorphism (crystal)
Precipitation (chemical)
Pulverization
Solvents
(preparation of **crystalline** form of **nateglinide** for dosage forms)

IT **105816-04-4P, Nateglinide**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(preparation of **crystalline** form of **nateglinide** for dosage forms)

IT 56-23-5, Carbontetrachloride, processes 64-17-5, Ethanol, processes 64-19-7, Acetic acid, processes 67-56-1, Methanol, processes 67-63-0, Isopropanol, processes 67-64-1, Acetone, processes 67-66-3, Chloroform, processes 68-12-2, N,N-Dimethylformamide, processes 71-23-8, n-Propanol, processes 71-36-3, n-Butanol, processes 75-05-8,

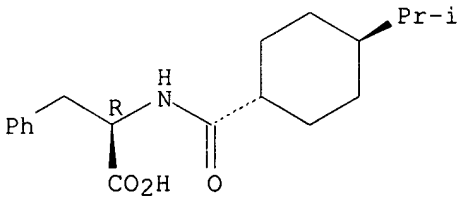
Acetonitrile, processes 75-09-2, Dichloromethane, processes 75-52-5, Nitromethane, processes 78-93-3, MEK, processes 107-06-2, 1,2-Dichloroethane, processes 108-10-1, Methyl isobutyl ketone 108-88-3, Toluene, processes 109-99-9, Tetrahydrofuran, processes 110-54-3, Hexane, processes 110-71-4 123-91-1, Dioxane, processes 127-19-5, N,N-Dimethylacetamide 141-78-6, Ethyl acetate, processes 142-82-5, Heptane, processes 563-80-4, Methyl isopropyl ketone 872-50-4, N-Methylpyrrolidone, processes 1330-20-7, Xylene, processes
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(preparation of **crystalline** form of **nateglinide** for dosage forms)

IT 673-06-3, D-Phenylalanine 84855-54-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **crystalline** form of **nateglinide** for dosage forms)

IT **105816-04-4P, Nateglinide**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(preparation of **crystalline** form of **nateglinide** for dosage forms)

RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:648496 HCAPLUS
DN 141:179640
ED Entered STN: 12 Aug 2004
TI Preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**
IN Frenkel, Gustavo; **Gome, Boaz**; Wizel, Shlomit
PA **Teva Pharmaceutical Industries Ltd., Israel**; **Teva Pharmaceuticals USA, Inc.**
SO PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0231-24
ICS C07C0233-63; A61K0031-16; A61P0003-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, **75**

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004067496	A1	20040812	WO 2004-US839	20040113 <--

```
     WO 2004067496        C2    20041209
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
     WO 2004009532        A1    20040129    WO 2003-US322375       20030718 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004181089        A1    20040916    US 2003-622905         20030718 <--
     US 2005090552        A1    20050428    US 2003-693166         20031023 <--
     US 2005014836        A1    20050120    US 2003-746697         20031224 <--
     CA 2513753           AA    20040812    CA 2004-2513753        20040113 <--
     EP 1511717           A1    20050309    EP 2004-701826         20040113 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI US 2003-442109P      P     20030123
     US 2003-449791P      P     20030224
     US 2003-479016P      P     20030616
     US 2003-622905       A2    20030718  <--
     WO 2003-US22375      A2    20030718
     US 2003-693166       A2    20031023
     US 2003-746697       A2    20031224
     US 2002-396904P      P     20020718  <--
     US 2002-413622P      P     20020925  <--
     US 2002-414199P      P     20020926  <--
     US 2002-423750P      P     20021105  <--
     US 2002-432093P      P     20021210  <--
     US 2002-432962P      P     20021212  <--
     US 2003-614266       A     20030703
     WO 2004-US839        W     20040113  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------   -----  ----------------------------------------------
 WO 2004067496    ICM    C07C0231-24
                  ICS    C07C0233-63; A61K0031-16; A61P0003-00
                  IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                         C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];
                         A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
                  IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                         [I,C*]; C07C0233-63 [I,A]
                  ECLA   C07C231/24; C07C233/63
 WO 2004009532    IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                         C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];
                         A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
                  ECLA   A61K031/16; A61K031/198; C07C231/02; C07C231/24;
                         C07C233/63
 US 2004181089    IPCI   C07C0233-30 [ICM,7]; C07C0233-00 [ICM,7,C*]
                  IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                         [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*];
                         C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02
                         [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*];
                         C07C0233-63 [I,A]
```

	NCL	562/450.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
US 2005090552	IPCI	C07C0233-87 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
US 2005014836	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-29 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
CA 2513753	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61P0003-00 [I,A]; A61P0003-00 [I,C*]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
EP 1511717	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]

AB The preparation of a polymorphic **crystalline** form (e.g., **form U**) of the antidiabetic agent **nateglinide** is described.

ST **nateglinide crystal** polymorphism antidiabetic

IT Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(C5-12, solvents; in the preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT **Crystallization**
Precipitation (chemical)
(in the preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT Antidiabetic agents
Polymorphism (crystal)
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT Diabetes mellitus
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide** for the treatment of)

IT Drug delivery systems
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide** for use in)

IT 141-78-6, Ethyl acetate, uses 142-82-5, Heptane, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(in the preparation of a polymorphic **crystalline** form of the

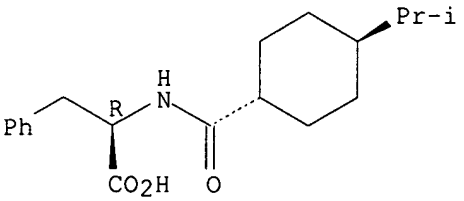
antidiabetic agent **nateglinide**)

IT **105816-04-4, Nateglinide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT **105816-04-4, Nateglinide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:203799 HCAPLUS
DN 140:241062
ED Entered STN: 14 Mar 2004
TI Process for the formation of a **crystalline** polymorphic form of nateglinide
IN Reguri, Buchi Reddy; Kadaboina, Rajasekhar; Polavarapu, Srinivas
PA Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0233-63
ICS C07C0231-24
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, **75**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004020396	A1	20040311	WO 2003-US26880	20030827 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003262928	A1	20040319	AU 2003-262928	20030827 <--
US 2004077725	A1	20040422	US 2003-649380	20030827 <--
PRAI IN 2002-MA631	A	20020828 <--		

WO 2003-US26880 W 20030827

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004020396	ICM	C07C0233-63
	ICS	C07C0231-24
	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
AU 2003262928	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
US 2004077725	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000

AB A **crystalline** polymorphic form of nateglinide are described and its X-ray diffraction pattern presented.

ST **crystal** polymorphism nateglinide

IT **Crystallization**
(in a process for the formation of a **crystalline** polymorphic form of nateglinide)

IT Drug delivery systems
(oral; process for the formation of a **crystalline** polymorphic form of nateglinide)

IT **Polymorphism (crystal)**
(process for the formation of a **crystalline** polymorphic form of nateglinide)

IT Aromatic hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; in a process for the formation of a **crystalline** polymorphic form of nateglinide)

IT Drug delivery systems
(tablets; process for the formation of a **crystalline** polymorphic form of nateglinide)

IT 95-47-6, o-Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for the formation of a **crystalline** polymorphic form of nateglinide)

IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); RCT (Reactant); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; RACT (Reactant or reagent); USES (Uses)
(process for the formation of a **crystalline** polymorphic form of nateglinide)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

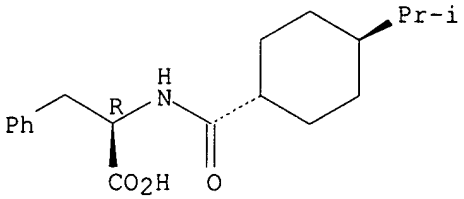
RE

(1) Alembic Ltd; WO 03022251 A 2003 HCAPLUS
(2) Biocon India Ltd; WO 03093222 A 2003 HCAPLUS
(3) Koguchi, Y; US 5463116 A 1995 HCAPLUS
(4) Koguchi, Y; WO 03087039 A 2003 HCAPLUS
(5) LI, G; CHINESE CHEMICAL LETTERS 2003, V14(7), P730 HCAPLUS
(6) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCAPLUS
(7) Novartis Pharma Gmbh; WO 03087038 A 2003 HCAPLUS

IT **105816-04-4P**, Nateglinide

RL: PRP (Properties); RCT (Reactant); **SPN (Synthetic preparation)** ; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; RACT (Reactant or reagent); USES (Uses)
(process for the formation of a **crystalline** polymorphic form of nateglinide)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:80637 HCAPLUS
DN 140:151932
ED Entered STN: 01 Feb 2004
TI Preparation of polymorphic forms of **nateglinide**
IN **Yahalomi, Ronit; Shapior, Evgeny; Dolitzky, Ben-zion; Gozlan, Yigael; Gome, Boaz**
PA **Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceutical Usa, Inc.**
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0231-24
ICS C07C0233-63; A61K0031-16; A61P0003-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): **75**

FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004009532	A1	20040129	WO 2003-US22375	20030718 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004152782	A1	20040805	US 2003-614266	20030703 <--
US 6861553	B2	20050301		
CA 2492644	AA	20040129	CA 2003-2492644	20030718 <--
AU 2003253971	A1	20040209	AU 2003-253971	20030718 <--
US 2004116526	A1	20040617	US 2003-623237	20030718 <--
EP 1467964	A1	20041020	EP 2003-765665	20030718 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

```
     US 2005014949          A1     20050120    US 2003-623290          20030718 <--
     US 2005075400          A1     20050407    US 2003-622999          20030718 <--
     CN 1723190             A      20060118    CN 2003-821921          20030718 <--
     JP 2006511614          T2     20060406    JP 2005-505521          20030718 <--
     CA 2513753             AA     20040812    CA 2004-2513753         20040113 <--
     WO 2004067496          A1     20040812    WO 2004-US839           20040113 <--
     WO 2004067496          C2     20041209
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
     EP 1511717             A1     20050309    EP 2004-701826          20040113 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI US 2002-396904P        P      20020718  <--
     US 2002-413622P        P      20020925  <--
     US 2002-414199P        P      20020926  <--
     US 2002-423750P        P      20021105  <--
     US 2002-432093P        P      20021210  <--
     US 2002-432962P        P      20021212  <--
     US 2003-442109P        P      20030123
     US 2003-449791P        P      20030224
     US 2003-479016P        P      20030616
     US 2003-614266         A      20030703
     US 2002-393495P        P      20020703  <--
     US 2003-622905         A      20030718  <--
     WO 2003-US22375        W      20030718
     US 2003-693166         A      20031023
     US 2003-746697         A      20031224
     WO 2004-US839          W      20040113  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 ---------------  -----  ----------------------------------------------
 WO 2004009532    ICM    C07C0231-24
                  ICS    C07C0233-63; A61K0031-16; A61P0003-00
                  IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                         C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];
                         A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
                  IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                         [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*];
                         C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00
                         [I,C*]; C07C0233-63 [I,A]
                  ECLA   A61K031/16; A61K031/198; C07C231/02; C07C231/24;
                         C07C233/63
 US 2004152782    IPCI   A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*];
                         C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]
                  IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                         [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*];
                         C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02
                         [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*];
                         C07C0233-63 [I,A]
                  NCL    514/563.000
                  ECLA   A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02;
                         C07C231/24; C07C233/63
 CA 2492644       IPCI   C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*];
                         A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63
                         [ICS,7]; C07C0233-00 [ICS,7,C*]
                  IPCR   A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185
                         [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*];
                         C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00
```

		[I,C*]; C07C0233-63 [I,A]
AU 2003253971	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
US 2004116526	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C231/02; C07C231/24
EP 1467964	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
US 2005014949	IPCI	C07D0417-04 [ICM,7]; C07D0417-00 [ICM,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]
	NCL	546/270.400
	ECLA	A61K031/198
US 2005075400	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-61 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000
	ECLA	C07C231/24; C07C233/63
CN 1723190	IPCI	C07C0231-24 [I,A]; C07C0231-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]; A61K0031-16 [I,A]; A61P0003-00 [I,A]
JP 2006511614	IPCI	C07C0231-24 [I,A]; C07C0231-00 [I,C*]; A61K0031-198 [I,A]; A61K0031-185 [I,C*]; A61P0003-10 [I,A]; A61P0003-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]
	FTERM	4C206/AA01; 4C206/AA04; 4C206/FA53; 4C206/KA16; 4C206/MA01; 4C206/MA04; 4C206/ZC35; 4H006/AA01; 4H006/AA02; 4H006/AA03; 4H006/AB27; 4H006/AD15; 4H006/BB11; 4H006/BB12; 4H006/BB14; 4H006/BB16; 4H006/BB17; 4H006/BB19; 4H006/BB20; 4H006/BB21; 4H006/BB25; 4H006/BB31; 4H006/BC50; 4H006/BC51; 4H006/BJ20; 4H006/BJ50; 4H006/BS10; 4H006/BV62
CA 2513753	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61P0003-00 [I,A]; A61P0003-00 [I,C*]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
WO 2004067496	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
EP 1511717	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];

A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
IPCR C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]

AB The invention discloses the preparation of 26 characterized forms of **nateglinide** (forms A, C, D, F, G, I, J, K, L, M, N, O, P, Q, T, U, V, Y, α, β, γ, δ, ε, σ, θ and Ω). Most of the forms are solvates (with the exception of forms L, P, U, α, δ and σ). Polymorphic forms are characterized by their mp, DSC, XRPD, FTIR; form interconversion is also discussed. For example, D-phenylalanine is reacted with trans-[[4-(isopropyl)cyclohexanee]carbonyl]chloride (i. NaOHaq; ii. H2SO4). The wet cake of **nateglinide** is dissolved in EtOAc, the aqueous phase is removed and the resulting solution heated to 50° under reduced pressure and added to hot heptane. The resulting solution is cooled and seeded with the B-form to afford the δ-form (33% yield).

ST polymorphic **nateglinide** blood sugar lowering prepn

IT Fluidized beds
(dryers; preparation of polymorphic forms of **nateglinide**)

IT Drying apparatus
(fluidized-bed; preparation of polymorphic forms of **nateglinide**)

IT Solvents
(**nateglinide** solvate; preparation of polymorphic forms of **nateglinide**)

IT **Crystal nucleation**
Crystallization
Human
Polymorphism (crystal)
Slurries
(preparation of polymorphic forms of **nateglinide**)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood, lowering, treatment; preparation of polymorphic forms of **nateglinide**)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 71-23-8, n-Propanol, uses 71-36-3, n-Butanol, uses 75-05-8, Acetonitrile, uses 75-52-5, Nitromethane, uses 78-93-3, Methyl ethyl ketone, uses 108-10-1, Methyl isobutyl ketone 108-88-3, Toluene, uses 110-54-3, Hexane, uses 141-78-6, Ethyl acetate, uses 142-82-5, Heptane, uses 563-80-4, Methyl isopropyl ketone 1330-20-7, Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**nateglinide** solvate; preparation of polymorphic forms of **nateglinide**)

IT 67-66-3, Chloroform, uses 109-99-9, Tetrahydrofuran, uses 123-91-1, Dioxane, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of polymorphic forms of **nateglinide**)

IT **105816-04-4P, Nateglinide**
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; RCT (Reactant); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; RACT (Reactant or reagent); USES (Uses)
(preparation of polymorphic forms of **nateglinide**)

IT **105816-04-4DP, Nateglinide**, polymorphs 651353-42-3P 651353-43-4P 651353-44-5P 651353-45-6P 651353-46-7P 651353-47-8P 651353-48-9P 651353-49-0P 651353-50-3P 651353-51-4P 651353-52-5P 651353-53-6P 651353-54-7P
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; **SPN (Synthetic preparation)**; THU

(Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(preparation of polymorphic forms of **nateglinide**)

IT 673-06-3, D-Phenylalanine 84855-54-9, trans-[[4-(Isopropyl)cyclohexane]carbonyl]chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of polymorphic forms of **nateglinide**)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

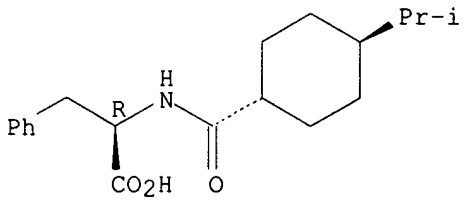
(1) Ajinomoto Co Inc; EP 1334963 A 2003 HCAPLUS
(2) Ajinomoto Co Inc; EP 1334964 A 2003 HCAPLUS
(3) Alembic Ltd; WO 03022251 A 2003 HCAPLUS
(4) Koguchi, Y; US 5463116 A 1995 HCAPLUS
(5) Koguchi, Y; WO 2003087039 2003 HCAPLUS
(6) Kumashiro, I; US 4816484 A 1989 HCAPLUS
(7) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCAPLUS
(8) Sumikawa, M; WO 2002034713 A 2002 HCAPLUS
(9) Takahashi, D; WO 2002032854 A 2002 HCAPLUS

IT **105816-04-4P, Nateglinide**
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; RCT (Reactant); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; RACT (Reactant or reagent); USES (Uses)
(preparation of polymorphic forms of **nateglinide**)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

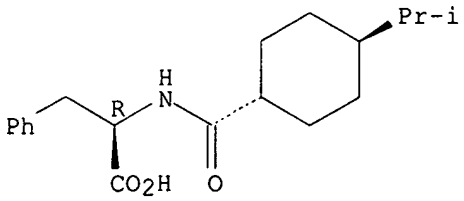


IT **105816-04-4DP, Nateglinide**, polymorphs
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(preparation of polymorphic forms of **nateglinide**)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:41431 HCAPLUS
DN 140:94292
ED Entered STN: 18 Jan 2004
TI Process for preparing **nateglinide** and its intermediates
IN **Yahalomi, Ronit; Shapiro, Evgeny; Dolitzky, Ben-zion; Gozlan, Yigael**
PA **Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.**
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0231-02
ICS C07C0231-24; C07C0233-63; C07C0051-60; C07C0061-08
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004005240	A1	20040115	WO 2003-US21238	20030703 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003256454	A1	20040123	AU 2003-256454	20030703 <--
	EP 1487782	A1	20041222	EP 2003-763310	20030703 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1671649	A	20050921	CN 2003-817439	20030703 <--
	US 2004116526	A1	20040617	US 2003-623237	20030718 <--
	US 2005014949	A1	20050120	US 2003-623290	20030718 <--
	US 2005075400	A1	20050407	US 2003-622999	20030718 <--
	CN 1723190	A	20060118	CN 2003-821921	20030718 <--
PRAI	US 2002-393495P	P	20020703 <--		
	US 2002-396904P	P	20020718 <--		
	US 2002-413622P	P	20020925 <--		
	US 2002-414199P	P	20020926 <--		
	US 2002-423750P	P	20021105 <--		
	US 2002-432093P	P	20021210 <--		
	US 2002-432962P	P	20021212 <--		
	US 2003-442109P	P	20030123		
	US 2003-449791P	P	20030224		
	US 2003-479016P	P	20030616		
	WO 2003-US21238	W	20030703		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004005240	ICM	C07C0231-02
	ICS	C07C0231-24; C07C0233-63; C07C0051-60; C07C0061-08
	IPCI	C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00

[ICS,7,C*]; C07C0051-60 [ICS,7]; C07C0051-58 [ICS,7,C*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C*]

IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]

ECLA A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24

AU 2003256454 IPCI C07C0231-02 [ICM,7]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; C07C0051-60 [ICS,7]; C07C0051-58 [ICS,7,C*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]

IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]

EP 1487782 IPCI C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; C07C0051-60 [ICS,7]; C07C0051-58 [ICS,7,C*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C*]

IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]

CN 1671649 IPCI C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; C07C0051-60 [ICS,7]; C07C0051-58 [ICS,7,C*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C*]

IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]

US 2004116526 IPCI A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]

IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]

NCL 514/563.000

ECLA A61K031/16; A61K031/198; C07C231/02; C07C231/24

US 2005014949 IPCI C07D0417-04 [ICM,7]; C07D0417-00 [ICM,7,C*]

IPCR A61K0031-185 [I,C*]; A61K0031-198 [I,A]

NCL 546/270.400

ECLA A61K031/198

US 2005075400 IPCI A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-61 [ICS,7]; C07C0233-00 [ICS,7,C*]

IPCR C07C0233-00 [I,C*]; C07C0233-63 [I,A]

NCL 514/563.000

ECLA C07C231/24; C07C233/63

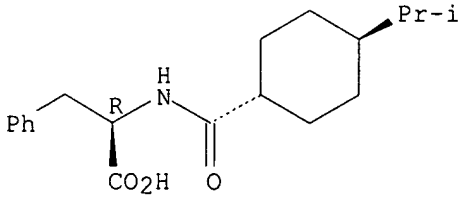
CN 1723190 IPCI C07C0231-24 [I,A]; C07C0231-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]; A61K0031-16 [I,A]; A61P0003-00 [I,A]

OS CASREACT 140:94292

AB A process for the preparation of **nateglinide** involves converting trans-4-isopropylcyclohexanecarboxylic acid into the acid chloride by reaction with thionyl chloride in the presence of an organic amide and acylation of a suitable salt of D-phenylalanine with the acid chloride in

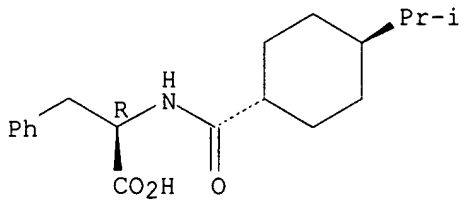
a single or two phase system or in water free of a co-solvent.
ST **nateglinide** prepn; isopropylcyclohexanecarboxylic acid chloride prepn acylation phenylalanine
IT **105816-04-4P, Nateglinide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(process for preparation of **nateglinide**)
IT 673-06-3, D Phenylalanine 7077-05-6, trans-4 Isopropylcyclohexanecarboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparation of **nateglinide**)
IT 84855-54-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparation of **nateglinide**)
IT **173653-89-9**
RL: PRP (Properties)
(properties of **nateglinide** hydrate)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Kk; EP 1334963 A 2003 HCAPLUS
(2) Koguchi, Y; US 5463116 A 1995 HCAPLUS
(3) Kumashiro, I; US 4816484 A 1989 HCAPLUS
(4) Shinkai, H; JOURNAL OF MEDICINAL CHEMISTRY 1989, V32(7), P1436 HCAPLUS
(5) Takahashi, D; WO 2002032854 A 2002 HCAPLUS
(6) Zhu, X; HECHENG HUAXUE 2001, V9(6), P537 HCAPLUS
IT **105816-04-4P, Nateglinide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(process for preparation of **nateglinide**)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **173653-89-9**
RL: PRP (Properties)
(properties of **nateglinide** hydrate)
RN 173653-89-9 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



●x H_2O

L61 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:892741 HCAPLUS
DN 139:369757
ED Entered STN: 14 Nov 2003
TI Process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide)
IN Rajamahendra, Shanmughasamy; Aswathanarayanappa, Chandrashekar; Puthiaparampil, Tom Thomas; Sridharan, Madhavan; Ganesh, Sambasivam
PA Biocon India Limited, India
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0233-63
ICS A61K0031-198
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, **75**

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003093222	A1	20031113	WO 2002-IN114	20020429 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2481322	AA	20031113	CA 2002-2481322	20020429 <--
	AU 2002304281	A1	20031117	AU 2002-304281	20020429 <--
	EP 1499586	A1	20050126	EP 2002-733208	20020429 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2005165108	A1	20050728	US 2003-508364	20020429 <--
	JP 2005523933	T2	20050811	JP 2004-501362	20020429 <--
PRAI	WO 2002-IN114	W	20020429 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003093222	ICM	C07C0233-63
	ICS	A61K0031-198

	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; A61P0003-00 [I,C*]; A61P0003-10 [I,A]; C07B0053-00 [N,A]; C07B0053-00 [N,C*]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]; C07C0235-00 [I,C*]; C07C0235-82 [I,A]
CA 2481322	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]
AU 2002304281	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; A61P0003-00 [I,C*]; A61P0003-10 [I,A]; C07B0053-00 [N,A]; C07B0053-00 [N,C*]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]; C07C0235-00 [I,C*]; C07C0235-82 [I,A]
EP 1499586	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; A61P0003-00 [I,C*]; A61P0003-10 [I,A]; C07B0053-00 [N,A]; C07B0053-00 [N,C*]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]; C07C0235-00 [I,C*]; C07C0235-82 [I,A]
US 2005165108	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0235-82 [ICS,7]; C07C0235-00 [ICS,7,C*]
	NCL	514/563.000
JP 2005523933	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]; C07C0231-02 [ICS,7]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07B0053-00 [ICS,7]; C07M0007-00 [ICS,7]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; A61P0003-00 [I,C*]; A61P0003-10 [I,A]; C07B0053-00 [N,A]; C07B0053-00 [N,C*]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]; C07C0235-00 [I,C*]; C07C0235-82 [I,A]
	FTERM	4C206/AA04; 4C206/FA53; 4C206/ZC35; 4H006/AA01; 4H006/AA02; 4H006/AA03; 4H006/AB27; 4H006/AB84; 4H006/AC53; 4H006/AC81; 4H006/AD15; 4H006/BA92; 4H006/BB12; 4H006/BB31; 4H006/BJ20; 4H006/BS10; 4H006/BV24

AB Novel polymorph Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I; i.e., nateglinide) is produced having a different IR spectrum and X-ray diffraction patterns (presented) from previously known forms of I.

ST nateglinide prepn **crystal** polymorphism; isopropylcyclohexylcarbonylphenylalanine prepn **crystal** polymorphism

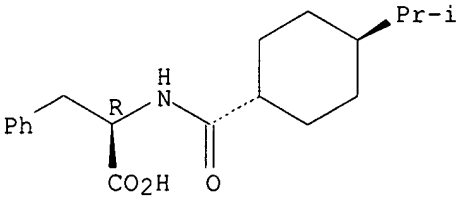
IT Drying
Filtration
(in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Acids, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(inorg.; in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT Diabetes mellitus
(non-insulin-dependent; process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide) for the treatment of)
IT Antidiabetic agents
Polymorphism (crystal)
(process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT Ligroine
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT 1344-28-1, Alumina, uses
RL: NUU (Other use, unclassified); USES (Uses)
(base support; in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT 110-86-1, Pyridine, reactions 121-44-8, Triethylamine, reactions 497-19-8, Sodium carbonate, reactions 584-08-7, Potassium carbonate 1310-58-3, Potassium hydroxide, reactions 1310-65-2, Lithium hydroxide 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT 7077-05-6, trans-4-Isopropylcyclohexanecarboxylic acid 13033-84-6, D-Phenylalanine methyl ester hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT 71760-04-8, Propanephosphonic acid anhydride
RL: RGT (Reagent); RACT (Reactant or reagent)
(mineral acid; in a process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT **105816-04-4P**, Nateglinide
RL: **IMF (Industrial manufacture)**; **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PREP (Preparation)**; **PROC (Process)**
(process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 75-09-2, Dichloromethane, uses 141-78-6, Ethyl acetate, uses 1300-21-6, Dichloroethane 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co Inc; EP 196222 B1 1986
(2) Ajinomoto Co Inc; US 4816484 A 1986 HCAPLUS
(3) Li, G; Yaowu Fenxi Zazhi 2001, V21(5), P342 HCAPLUS

(4) Shinkai, H; Journal of Medicinal Chemistry 1989, V32(7), P1436 HCAPLUS
(5) Sumikawa; US 5463116 A 1995 HCAPLUS
IT **105816-04-4P**, Nateglinide
RL: **IMF (Industrial manufacture)**; **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PREP (Preparation)**; **PROC (Process)**
(process for the preparation of a **crystal** polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:837030 HCAPLUS
DN 139:341723
ED Entered STN: 24 Oct 2003
TI Novel nateglinide **crystals**
IN Koguchi, Yoshihito; Nakao, Tomoko; Sumikawa, Michito
PA Ajinomoto Co., Inc., Japan
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C0233-63
ICS C07C0231-24
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): **75**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003087039	A1	20031023	WO 2003-JP4686	20030414 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003236243	A1	20031027	AU 2003-236243	20030414 <--
	EP 1496048	A1	20050112	EP 2003-746474	20030414 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	US 2005101672	A1	20050512	US 2004-965171	20041015 <--
PRAI	JP 2002-111963	A	20020415 <--		

WO 2003-JP4686 W 20030414

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003087039	ICM	C07C0233-63
	ICS	C07C0231-24
	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
AU 2003236243	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
EP 1496048	IPCI	C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
US 2005101672	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-76 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0233-00 [I,C*]; C07C0233-76 [I,A]
	NCL	514/563.000
	ECLA	C07C233/63

AB A type **crystal** (powder X-ray diffraction main peaks: 4.4°, 5.2°, 15.7°, 18.5° (2 theta)), M type **crystal** (powder X-ray diffraction main peaks: 6.0°, 14.2°, 15.2°, 18.8° (2 theta)), and P type **crystal** (powder X-ray diffraction main peaks: 4.8°, 5.3°, 14.3°, 15.2° (2 theta)) of nateglinide, which are all novel **crystals**, can be prepared by a method comprising dissolving nateglinide in a solvent exhibiting high solubility for nateglinide and then adding a solvent exhibiting poor solubility for nateglinide or dissolving nateglinide in a mixed solvent comprising a solvent exhibiting high solubility for nateglinide and a solvent exhibiting poor solubility for nateglinide and then cooling the resulting nateglinide solution to precipitate **crystals**, subjecting the product to filtration, and then drying at a specific temperature Nateglinide is a known antidiabetic.

ST nateglinide **crystal** prepn antidiabetic

IT **Crystal structure**
(**crystal** structure of nateglinide **crystals**)

IT Antidiabetic agents
Crystal structure types
Drying
Polymorphism (crystal)
(preparation of A, M, and P type nateglinide **crystals** and drying of said **crystals**)

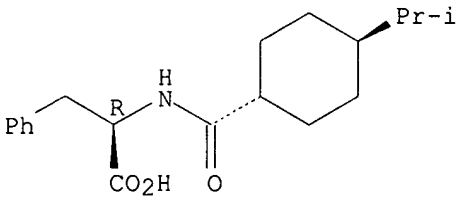
IT **Crystallization**
(preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)

IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); **PUR (Purification or recovery)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)

IT 64-17-5, Ethanol, uses 67-64-1, Acetone, uses 75-09-2, Methylene chloride, uses 110-54-3, Hexane, uses 123-91-1, Dioxane, uses

7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent for **crystallization**; preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co Inc; JP 05-208943 A 1993 HCAPLUS
(2) Ajinomoto Co Inc; BR 1100807 A3 1993
(3) Ajinomoto Co Inc; ES 2100291 T3 1993 HCAPLUS
(4) Ajinomoto Co Inc; CA 2114678 A 1993 HCAPLUS
(5) Ajinomoto Co Inc; EP 526171 A2 1993 HCAPLUS
(6) Ajinomoto Co Inc; US 5463116 A 1993 HCAPLUS
(7) Ajinomoto Co Inc; US 5488150 A 1993 HCAPLUS
(8) Ajinomoto Co Inc; DE 69217762 E 1993
(9) Ajinomoto Co Inc; WO 0234713 A1 2002 HCAPLUS
(10) Anon; AU 200196001 A
IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); **PUR (Purification or recovery)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 9 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:837029 HCAPLUS
DN 139:328379
ED Entered STN: 24 Oct 2003
TI **Crystal** polymorphism of nateglinide
IN Sutton, Paul Allen
PA Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SO PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C0233-63
ICS C07C0231-22
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, **75**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003087038	A1	20031023	WO 2003-EP3864	20030414 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU,

```
            LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC,
            SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW
         RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE,
            DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
            SI, SK, TR
    CA 2482669          AA    20031023    CA 2003-2482669        20030414 <--
    AU 2003242520       A1    20031027    AU 2003-242520         20030414 <--
    EP 1497258          A1    20050119    EP 2003-746296         20030414 <--
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
    BR 2003009210       A     20050209    BR 2003-9210           20030414 <--
    CN 1646481          A     20050727    CN 2003-808436         20030414 <--
    JP 2005522503       T2    20050728    JP 2003-583994         20030414 <--
    US 2005256336       A1    20051117    US 2004-510927         20041102 <--
PRAI US 2002-372625P    P     20020415  <--
    WO 2003-EP3864      W     20030414
CLASS
 PATENT NO.      CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------  -----  ----------------------------------------------
 WO 2003087038   ICM    C07C0233-63
                 ICS    C07C0231-22
                 IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
                 ECLA   C07C231/22; C07C233/63
 CA 2482669      IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
 AU 2003242520   IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
 EP 1497258      IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
 BR 2003009210   IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
 CN 1646481      IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0231-22 [ICS,7]; C07C0231-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
 JP 2005522503   IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*];
                        C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*];
                        A61K0031-198 [ICS,7]; A61K0031-185 [ICS,7,C*];
                        C07M0007-00 [ICS,7]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
                        [I,C*]; C07C0233-63 [I,A]
                 FTERM  4C206/AA04; 4C206/FA53; 4C206/NA20; 4C206/ZC35;
                        4H006/AA01; 4H006/AA02; 4H006/AB27; 4H006/AD15;
                        4H006/BB11; 4H006/BB14; 4H006/BC51; 4H006/BJ20;
                        4H006/BJ50; 4H006/BS10; 4H006/BT22
 US 2005256336   IPCI   A61K0031-195 [ICM,7]; A61K0031-185 [ICM,7,C*];
                        C07C0235-70 [ICS,7]; C07C0235-00 [ICS,7,C*]
                 IPCR   A61K0031-185 [I,C*]; A61K0031-195 [I,A]; C07C0235-00
```

[I,C*]; C07C0235-70 [I,A]
NCL 562/450.000

AB New **crystal** forms of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (i.e., nateglinide) are produced by dissolving nateglinide in any of its forms, including solvates, in an organic solvent to form a solution followed by precipitation of nateglinide from the solution, and isolating and drying the precipitated **crystal** form of nateglinide. The precipitation of nateglinide may be induced either by cooling the solution, or by addition of another solvent which is miscible with the first solvent but in which nateglinide is only poorly soluble, or by combination of the two. Depending on the solvent a specific **crystal** form of nateglinide may be obtained, e.g., the R'-type **crystal** form of nateglinide produced by the described method has a different m.p., infra red spectra and X-ray diffraction patterns from the previously known **crystal** forms of nateglinide.

ST nateglinide **crystal** polymorphism

IT **Polymorphism (crystal)**
(**crystal** polymorphism of nateglinide)

IT Cooling
Drying
Precipitation (chemical)
(in producing the **crystal** polymorphism of nateglinide)

IT Mixing
(stirring; in producing the **crystal** polymorphism of nateglinide)

IT **105816-04-4**, Nateglinide
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PROC (Process)**
(**crystal** polymorphism of nateglinide)

IT 7732-18-5, Water, uses 9004-65-3, Hydroxypropylmethylcellulose
RL: NUU (Other use, unclassified); USES (Uses)
(nonsolvent; in the **crystal** polymorphism of nateglinide)

IT 64-17-5, Ethanol, uses 108-88-3, Toluene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in the **crystal** polymorphism of nateglinide)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

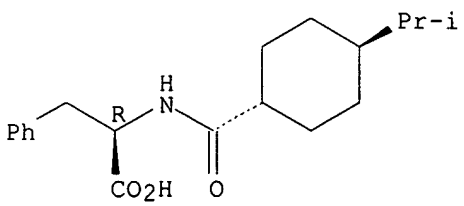
(1) Alembic Ltd; WO 03022251 A 2003 HCAPLUS
(2) LI, G; YAOXUE XUEBAO 2001, V36(7), P532 HCAPLUS
(3) Sumikawa, M; US 5463116 A 1995 HCAPLUS

IT **105816-04-4**, Nateglinide
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PROC (Process)**
(**crystal** polymorphism of nateglinide)

RN 105816-04-4 HCAPLUS

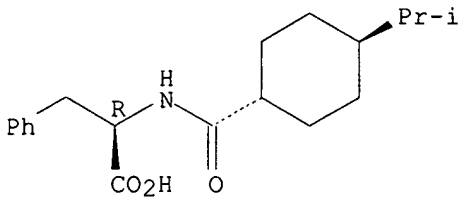
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:762699 HCAPLUS
DN 140:64875
ED Entered STN: 30 Sep 2003
TI Study of nateglinide polymorphism
AU Li, Gang; Xu, Qunwei; Yao, Jie; Su, Guoqiang; Wang, Fang
CS Chemistry and Physics Central- laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SO Huagong Shikan (**2002**), 16(7), 17-18
CODEN: HUSHFT; ISSN: 1002-154X
PB Huagong Shikan Zazhishe
DT Journal
LA Chinese
CC 63-5 (Pharmaceuticals)
AB The **crystal** structure of nateglinide called an S form determined by an x-ray powder diffraction method. The pattern, data, and **crystal** size were obtained. The m.p. was determined by DSC as 172.04°.
ST nateglinide polymorphism **crystal** structure
IT **Polymorphism (crystal)**
(nateglinide polymorphism)
IT **Crystal structure**
(of nateglinide polymorph)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nateglinide polymorphism)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nateglinide polymorphism)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

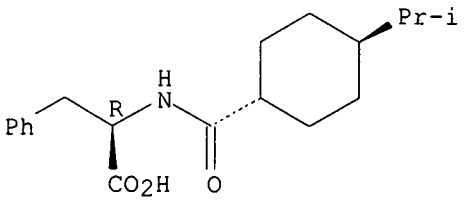
Absolute stereochemistry. Rotation (-).



L61 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:686087 HCAPLUS
DN 140:292376
ED Entered STN: 03 Sep 2003
TI Study on the **crystal** types of nateglinide
AU Sun, Piaoyang; Gou, Shaohua; Ma, Yonglin
CS State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, 210093, Peop. Rep. China
SO Huaxue Yanjiu Yu Yingyong (**2002**), 14(4), 457-458, C3
CODEN: HYYIFM; ISSN: 1004-1656
PB Huaxue Yanjiu Yu Yingyong Bianjibu
DT Journal

LA Chinese
CC 63-5 (Pharmaceuticals)
AB N-(trans-4-methylethylcyclohexylcarbonyl)-D-phenylalanine, nateglinide, is an effective drug to decrease blood sugar, which is under clin. trials in China. This compound has been reported to have two **crystal** types, one of which is more suitable to prepare the drug. The nateglide with different **crystal** types was prepared Their m.ps., TGA-DTA and DSC spectral data, LR and X-ray powder diffraction spectra of all samples were studied with different **crystal** types. A new **crystal** type that has not been reported in the literature was discovered. The method for controlling the **crystal** type was also presented.
ST nateglide polymorphism antidiabetic
IT Antidiabetic agents
Crystal morphology
Crystal structure
Human
Polymorphism (crystal)
(polymorphism of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymorphism; polymorphism of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymorphism; polymorphism of nateglinide)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:221492 HCAPLUS
DN 138:243310
ED Entered STN: 21 Mar 2003
TI Novel stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and process of preparation
IN Shah, Vrajesh; Hitkari, Anurag; Deo, Keshav; Rengaraju, Srinivasan
PA Alembic Limited, India
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K0009-14
ICS A61K0009-16; C07C0229-00
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

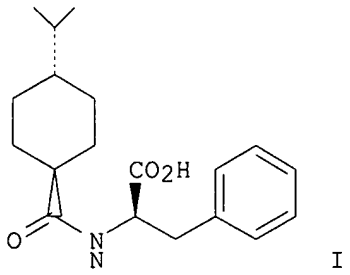
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2003022251 A1 20030320 WO 2001-IB2080 20011105 <--
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, ES, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
IN 191354 A 20031129 IN 2001-MU872 20010912 <--
EP 1435912 A1 20040714 EP 2001-978760 20011105 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRAI IN 2001-MU871 A 20010912 <--
IN 2001-MU872 A 20010912 <--
WO 2001-IB2080 W 20011105 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003022251	ICM	A61K0009-14
	ICS	A61K0009-16; C07C0229-00
	IPCI	A61K0009-14 [ICM,7]; A61K0009-16 [ICS,7]; C07C0229-00 [ICS,7]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C233/63
IN 191354	IPCI	C07C0101-34 [ICM,7]; A61K0031-195 [ICS,7]; A61K0031-185 [ICS,7,C*]
EP 1435912	IPCI	A61K0009-14 [ICM,7]; A61K0009-16 [ICS,7]; C07C0229-00 [ICS,7]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]

GI



I

AB A stable **crystal** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) may be produced by **crystallization** of I with a solvent at 25 - 38 °C and forming **crystals** in the solvent. The **crystal** form may be formed by **recrystn.** out of solution The **crystal** form obtained in this way have different m.p., infra red spectrum and X-ray diffraction patterns from previously known forms "B-type" and "H-Type" of the compound

ST phenylalanine isopropylcyclohexylcarbonyl **crystal** form

IT **Crystal structure**
(of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **Crystal morphology**
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **105816-04-4**
RL: **PEP (Physical, engineering or chemical process)**; PRP

(Properties); **PYP (Physical process)**; THU (Therapeutic use);
BIOL (Biological study); **PROC (Process)**; USES (Uses)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

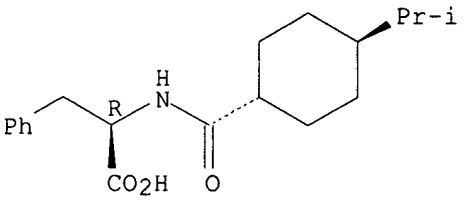
IT 68-12-2, Dmf, processes 75-05-8, Acetonitrile, processes 127-19-5, Dimethylacetamide
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Sumikawa; US 5463116 A 1995 HCAPLUS

IT **105816-04-4**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 13 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:62632 HCAPLUS
DN 138:73015
ED Entered STN: 28 Jan 2003
TI Synthesis process for trans-4-isopropylcyclohexanecarboxylic acid
IN Gu, Lianquan; An, Linkun; Ma, Lin; Guo, Xindong; Huang, Zhishu
PA Zhongshan Univ., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
IC ICM C07C0061-08
ICS C07C0051-36
CC 24-5 (Alicyclic Compounds)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1319583	A	20011031	CN 2001-107459	20010116 <--
PRAI CN 2001-107459		20010116 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
CN 1319583	ICM	C07C0061-08
	ICS	C07C0051-36
	IPCI	C07C0061-08 [ICM,7]; C07C0061-00 [ICM,7,C*];

C07C0051-36 [ICS,7]; C07C0051-347 [ICS,7,C*]
IPCR C07C0051-347 [I,C*]; C07C0051-36 [I,A]; C07C0061-00 [I,C*]; C07C0061-08 [I,A]

OS CASREACT 138:73015

AB The process comprises hydrogenating cumic acid in acetic acid in the presence of PtO_2, recovering solvent, treating with 10-35% inorg. base (such as $Ba(OH)_2$, $Mg(OH)_2$, KOH, or NaOH) solution at 50-150° for 10-20 h, neutralizing with HCl to pH 2, **crystallizing**, filtering, and **recrystg**. in methanol.

ST isopropylcyclohexanecarboxylic acid prepn

IT Isomerization
Isomerization catalysts
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid via isomerization with base)

IT Bases, uses
RL: CAT (Catalyst use); USES (Uses)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid via isomerization with base)

IT 1309-42-8, Magnesium hydroxide 1310-58-3, Potassium hydroxide, uses 1310-73-2, Sodium hydroxide, uses 1314-15-4, Platinum dioxide 17194-00-2, Barium hydroxide
RL: CAT (Catalyst use); USES (Uses)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

IT **105816-04-4P**, Nateglinide
RL: **PNU (Preparation, unclassified); PREP (Preparation)**
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

IT 536-66-3, Cumic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

IT 62067-45-2P, 4-Isopropylcyclohexanecarboxylic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

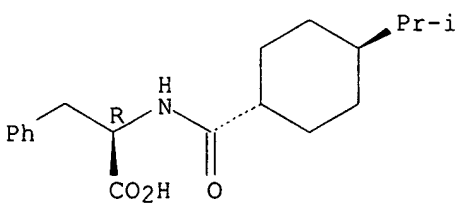
IT 7077-05-6P, trans-4-Isopropylcyclohexanecarboxylic acid
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

IT **105816-04-4P**, Nateglinide
RL: **PNU (Preparation, unclassified); PREP (Preparation)**
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:813874 HCAPLUS
DN 137:311199
ED Entered STN: 25 Oct 2002
TI Amino acid complexes of C-aryl glucosides for treatment of diabetes
IN Gougoutas, Jack Z.
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 33, 63, **75**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002083066	A2	20021024	WO 2002-US11066	20020408 <--
	WO 2002083066	A3	20030306		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2444481	AA	20021024	CA 2002-2444481	20020408 <--
	US 2003064935	A1	20030403	US 2002-117914	20020408 <--
	US 6774112	B2	20040810		
	EP 1385856	A2	20040204	EP 2002-723801	20020408 <--
	EP 1385856	B1	20060222		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004536047	T2	20041202	JP 2002-580871	20020408 <--
	AT 318272	E	20060315	AT 2002-723801	20020408 <--
PRAI	US 2001-283097P	P	20010411 <--		
	WO 2002-US11066	W	20020408 <--		

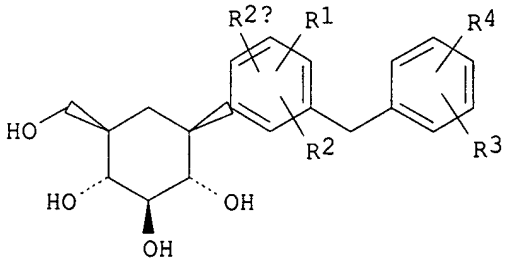
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002083066	ICM	A61K
	IPCI	A61K [ICM,7]
	IPCR	A61K0031-351 [I,A]; A61K0031-351 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; C07D0309-00 [I,C*]; C07D0309-10 [I,A]; C07H0015-00 [I,C*]; C07H0015-203 [I,A]
	ECLA	A61K031/351+M; A61K045/06; C07H015/203
CA 2444481	IPCI	C07H0007-04 [ICM,7]; C07H0007-00 [ICM,7,C*]; A61K0031-70 [ICS,7]
	IPCR	A61K0031-351 [I,A]; A61K0031-351 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; C07D0309-00 [I,C*]; C07D0309-10 [I,A]; C07H0015-00 [I,C*]; C07H0015-203 [I,A]
	ECLA	A61K031/351+M; A61K045/06; C07H015/203
US 2003064935	IPCI	A61K0031-70 [ICM,7]; C07H0005-06 [ICS,7]; C07H0005-00 [ICS,7,C*]
	IPCR	A61K0031-351 [I,A]; A61K0031-351 [I,C*]; A61K0045-00

		[I,C*]; A61K0045-06 [I,A]; C07H0015-00 [I,C*]; C07H0015-203 [I,A]
	NCL	514/023.000
	ECLA	A61K031/351+M; A61K045/06; C07H015/203
EP 1385856	IPCI	C07H0007-00 [I,C]; A61K0031-70 [I,C]; C07H0007-04 [I,A]; A61K0031-70 [I,A]
	IPCR	A61K0031-351 [I,C*]; A61K0045-00 [I,C*]; C07D0309-00 [I,C*]; C07H0015-00 [I,C*]; A61K0031-351 [I,A]; A61K0045-06 [I,A]; C07D0309-10 [I,A]; C07H0015-203 [I,A]
	ECLA	A61K031/351+M; A61K045/06; C07H015/203
JP 2004536047	IPCI	C07H0007-04 [ICM,7]; C07H0007-00 [ICM,7,C*]; A61K0031-7004 [ICS,7]; A61P0003-04 [ICS,7]; A61P0003-06 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]; A61P0009-10 [ICS,7]; A61P0009-12 [ICS,7]; A61P0009-00 [ICS,7,C*]; A61P0013-12 [ICS,7]; A61P0013-00 [ICS,7,C*]; A61P0017-02 [ICS,7]; A61P0017-00 [ICS,7,C*]; A61P0027-02 [ICS,7]; A61P0027-00 [ICS,7,C*]
	IPCR	A61K0031-351 [I,A]; A61K0031-351 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; C07D0309-00 [I,C*]; C07D0309-10 [I,A]; C07H0015-00 [I,C*]; C07H0015-203 [I,A]
	FTERM	4C057/BB02; 4C057/DD01; 4C057/EE04; 4C086/AA01; 4C086/AA02; 4C086/AA03; 4C086/EA01; 4C086/GA15; 4C086/MA01; 4C086/MA02; 4C086/MA04; 4C086/MA05; 4C086/MA06; 4C086/MA10; 4C086/NA14; 4C086/ZA42; 4C086/ZA70; 4C086/ZA81; 4C086/ZA89; 4C086/ZC33; 4C086/ZC35
AT 318272	IPCI	C07H0007-04 [ICS,7]; C07H0007-00 [ICS,7,C*]; A61K0031-70 [ICS,7]
	IPCR	A61K0031-351 [I,C*]; A61K0045-00 [I,C*]; C07D0309-00 [I,C*]; C07H0015-00 [I,C*]; A61K0031-351 [I,A]; A61K0045-06 [I,A]; C07D0309-10 [I,A]; C07H0015-203 [I,A]
	ECLA	A61K031/351+M; A61K045/06; C07H015/203

OS MARPAT 137:311199

GI



I

AB **Crystalline** complexes are obtained from 1:1 or 2:1 mixts. of either the (D) or (L) enantiomer of natural amino acids and compds. of formula I [R1, R2, R2a = H, OH, OR5, alkyl, OCHF2, OCF3, SR5a, halogen; R3, R4 = H, OH, OR5b, alkyl, cycloalkyl, CF3, OCHF2, OCF3, halogen, CONR6R6a, CO2R5c, CO2H, COR6b, CH(OH)R6c, CH(OR5d)R6d, CN, NHCOR5e, NHSO2R5f, NHSO2-aryl, SR5g, SOR5h, SO2R5i, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms (N, O, S, SO, and/or SO2), or R3 and R4

together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring; R5, R5a-R5i are independently alkyl; R6, R6a-R6d are independently H, alkyl, aryl, alkylaryl or cycloalkyl, or NR6R6a form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring]. A method is also provided for treating diabetes and related diseases employing an SGLT2 (sodium dependent glucose transporters found in the intestine and kidney) inhibiting amount of the above complex alone or in combination with another antidiabetic agent or other therapeutic agent. Thus, I (R1 = 4-Me, R4 = 4-OCHF2, R2, R2a, R3 = H) was prepared by a multistep procedure starting from o-toluic acid, anisole, 2,3,4,6-tetra-O-benzyl-β-D-glucolactone, and CHF2Cl and treated with L-phenylalanine to form the **crystalline** 1:1 complex.

ST **crystal** structure amino acid complex aryl glucoside; amino acid complex aryl glucoside prepn antidiabetic

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Wound healing
(delayed; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Kidney, disease
(diabetic nephropathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Nerve, disease
(diabetic neuropathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Eye, disease
(diabetic retinopathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Fatty acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elevated blood levels; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Metabolic disorders
(metabolic syndrome X; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Antidiabetic agents
Antiobesity agents
Atherosclerosis
Crystal structure
Diabetes mellitus
Human
Hyperglycemia
Hypertension
Hypertriglyceridemia
Hypolipemic agents
Obesity
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT High-density lipoproteins
Hyperlipidemia
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 56-81-5, Glycerol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elevated blood levels; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 472968-85-7P 472968-86-8P 472968-87-9P 472968-88-0P 472968-89-1P
472968-90-4P 472968-91-5P 472968-93-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 75-45-6, Freon 22 100-66-3, Anisole, reactions 100-68-5, Thioanisole
118-90-1, o Toluic acid 1585-07-5, p-Bromoethylbenzene 3132-99-8, m Bromobenzaldehyde 13096-62-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 79669-49-1P 333359-79-8P 333359-87-8P 333359-88-9P 333360-85-3P
333360-86-4P 333360-87-5P 333360-88-6P 333361-13-0P 333361-15-2P
333361-21-0P 333361-30-1P 333361-33-4P 333361-35-6P 333361-37-8P
472968-94-8P 472968-95-9P 472968-96-0P 472968-97-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

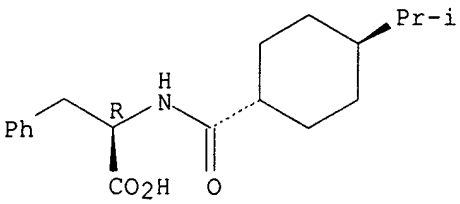
IT 51-64-9, Dexamphetamine 94-20-2, Chlorpropamide 122-09-8, Phentermine
637-07-0, Clofibrate 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol
25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate
56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin
79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone **105816-04-4**, Nateglinide
106650-56-0, Sibutramine 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide
141750-63-2, Nisvastatin 141758-74-9, AC2993 144288-97-1, TS 962
145599-86-6, Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427 159183-92-3, L750355 161600-01-7, Isaglitazone 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9, NN-2344 199914-96-0, YM-440
213252-19-8, KRP297 244081-42-3, AJ9677 282526-98-1, ATL-962
287714-41-4, Rosuvastatin 335149-08-1, L895645 335149-14-9, R-119702
335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544
335149-23-0, NVPDPP-728A 335149-25-2, CP331648 430433-17-3, Glipyride
444069-80-1, Axokine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT **105816-04-4**, Nateglinide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

RN 105816-04-4 HCAPLUS

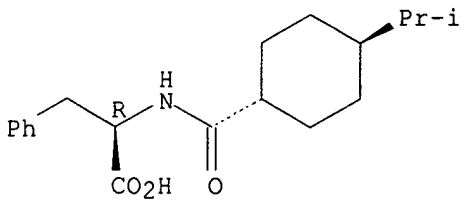
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



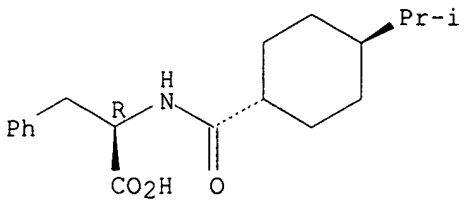
L61 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:811385 HCAPLUS
DN 139:12440
ED Entered STN: 25 Oct 2002
TI Identification of nateglinide and its **crystal** forms in nateglinide tablets using IR Spectra subtraction techniques
AU Lin, Kejiang; Chen, Wei; Tang, Weiguo; You, Qidong
CS Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 21009, Peop. Rep. China
SO Zhongguo Yaoke Daxue Xuebao (**2002**), 33(2), 124-126
CODEN: ZHYXE9; ISSN: 1000-5048
PB Zhongguo Yaoke Daxue
DT Journal
LA Chinese
CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 63
AB The innovational identification method of IR (eliminated method) for detection of the **crystal** form of nateglinide in prepns. was presented. The IR spectrum by spectra subtraction techniques was obtained by subtracting IR spectrum after adding small volume of solvent to eliminate nateglinide from the spectrum of nateglinide tablets' KBr disk to identify the **crystal** form of nateglinide. The method (eliminated method) was useful in identification of the nateglinide **crystal** form in prepns.
ST nateglinide tablet **crystal** form IR spectra
IT **Crystal morphology**
IR spectra
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)
IT Drug delivery systems
(tablets; identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)
IT **105816-04-4**, Nateglinide
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)
IT **105816-04-4**, Nateglinide
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:609152 HCAPLUS
DN 138:254901
ED Entered STN: 15 Aug 2002
TI a new synthesis method of nateglinide as antidiabetic drug
AU Wang, Dun; Liang, Yiheng; Gong, Ping; Zhao, Yanfang
CS School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop. Rep. China
SO Zhongguo Yaowu Huaxue Zazhi (**2002**), 12(2), 94-96
CODEN: ZYHZEF; ISSN: 1005-0108
PB Zhongguo Yaowu Huaxue Zazhi Bianjibu
DT Journal
LA Chinese
CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 63
OS CASREACT 138:254901
AB A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene by Friedel-Crafts reaction, chloroform reaction, catalytic hydrogenation to obtain trans-4-isopropylhexanecarboxylic acid, acylation of D-phenylalanine Et ester, hydrolysis to obtain nateglinide B-type **crystal**, and **crystal**-conversion. The total yield was 9.8%.
ST nateglinide antidiabetic drug synthesis
IT Antidiabetic agents
(of nateglinide and synthesis thereof)
IT **Crystal structure types**
(type B; of nateglinide as antidiabetic drug)
IT 63-91-2, L-Phenylalanine, reactions 75-36-5, Acetyl chloride 98-82-8, Isopropylbenzene 524-38-9 3081-24-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of nateglinide as antidiabetic drug)
IT 536-66-3P, 4-Isopropylbenzoic acid 645-13-6P, 4-Isopropylacetophenone 7077-05-6P, trans-4-Isopropylcyclohexanecarboxylic acid 508170-82-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of nateglinide as antidiabetic drug)
IT **105816-04-4P**, Nateglinide
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(synthesis of nateglinide as antidiabetic drug)
IT **105816-04-4P**, Nateglinide
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(synthesis of nateglinide as antidiabetic drug)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:391524 HCAPLUS
DN 136:374894
ED Entered STN: 24 May 2002
TI Nateglinide-containing hydrophilic drug preparations
IN Ninomiya, Nobutaka; Makino, Chisato; Yabuki, Akira
PA Ajinomoto Co., Inc., Japan
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM A61K0031-198
ICS A61K0009-20; A61K0009-28; A61K0047-10; A61K0047-26; A61K0047-38; A61P0003-10
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002040010	A1	20020523	WO 2001-JP9292	20011023 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001096000	A5	20020527	AU 2001-96000	20011023 <--
	CA 2426764	AA	20030423	CA 2001-2426764	20011023 <--
	BR 2001014897	A	20030812	BR 2001-14897	20011023 <--
	EP 1334721	A1	20030813	EP 2001-976818	20011023 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004029968	A1	20040212	US 2003-420886	20030423 <--
PRAI	JP 2000-324374	A	20001024 <--		
	WO 2001-JP9292	W	20011023 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002040010	ICM	A61K0031-198
	ICS	A61K0009-20; A61K0009-28; A61K0047-10; A61K0047-26; A61K0047-38; A61P0003-10
	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*];

		A61K0031-198 [I,A]
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6F2; A61K009/28H6F2; A61K009/28H6D; A61K031/198
AU 2001096000	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
CA 2426764	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0047-10 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]; A61K0009-20 [ICS,7]; A61K0047-26 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-38 [ICS,7]
BR 2001014897	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
EP 1334721	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6B; A61K009/20H6F2; A61K009/28H6D; A61K009/28H6F2; A61K031/198
US 2004029968	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0235-78 [ICS,7]; C07C0235-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
	NCL	514/563.000
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6B; A61K009/20H6F2; A61K009/28H6D; A61K009/28H6F2; A61K031/198

AB Hydrophilic drug prepns. contain nateglinide B **crystals** useful as a hypoglycemic agent as the active ingredient which comprises a hydrophilic substance selected from the group consisting of hydrophilic polymers, surfactants, sugars, sugar alcs. and salts, and thus have a contact angle of the preparation surface to water of 111° or less. These prepns., which are rapid release prepns. having high elution properties, can be easily produced.

ST nateglinide drug formulation

IT **Crystals**
(hypoglycemic hydrophilic drug prepns. containing nateglinide)

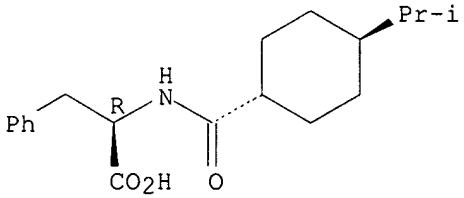
IT Antidiabetic agents
(nateglinide-containing hydrophilic drug prepns. as)

IT Surfactants
(nateglinide-containing hydrophilic drug prepns. containing)

IT Alditols
Carbohydrates, biological studies
Polymers, biological studies
Salts, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(nateglinide-containing hydrophilic drug prepns. containing)

IT Contact angle
(of nateglinide-containing hydrophilic drug prepns.)
IT **105816-04-4**, Nateglinide
RL: **BCP (Biochemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(hypoglycemic hydrophilic drug prepns. containing)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co Inc; JP 05208943 A 1993 HCAPLUS
(2) Ajinomoto Co Inc; EP 526171 A2 1993 HCAPLUS
(3) Ajinomoto Co Inc; US 5463116 A 1993 HCAPLUS
(4) Ajinomoto Co Inc; US 5488150 A 1993 HCAPLUS
(5) Ajinomoto Co Inc; JP 10194969 A 1999 HCAPLUS
(6) Ajinomoto Co Inc; US 9143323 A 1999
(7) Ajinomoto Co Inc; EP 965339 A1 1999 HCAPLUS
(8) Ajinomoto Co Inc; WO 9822105 A1 1999 HCAPLUS
(9) Nissan Chemical Industries Ltd; JP 06183955 A 1994 HCAPLUS
(10) Shin-Etsu Chemical Co Ltd; JP 07324101 A 1995 HCAPLUS
IT **105816-04-4**, Nateglinide
RL: **BCP (Biochemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(hypoglycemic hydrophilic drug prepns. containing)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:332157 HCAPLUS
DN 136:340998
ED Entered STN: 03 May 2002
TI Process for producing B-form nateglinide **crystals**
IN Sumikawa, Michito; Maruo, Makoto; Miyazaki, Kazuo; Nishina, Shigehiro; Matsuzawa, Yukiko
PA Ajinomoto Co., Inc., Japan
SO PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C0233-63
ICS C07C0227-42
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, **75**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002034713	A1	20020502	WO 2001-JP9293	20011023 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

```
            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
            US, UZ, VN, YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
    AU 2001096001        A5    20020506    AU 2001-96001          20011023 <--
    CA 2426745           AA    20030423    CA 2001-2426745        20011023 <--
    EP 1334964           A1    20030813    EP 2001-976819         20011023 <--
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
    BR 2001014846        A     20040225    BR 2001-14846          20011023 <--
    RU 2275354           C2    20060427    RU 2003-111948         20011023 <--
    US 2003229249        A1    20031211    US 2003-421888         20030424 <--
PRAI JP 2000-324375      A     20001024  <--
    WO 2001-JP9293       W     20011023  <--
CLASS
 PATENT NO.      CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------  -----  ----------------------------------------------
 WO 2002034713   ICM    C07C0233-63
                 ICS    C07C0227-42
                 IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0227-42 [ICS,7]; C07C0227-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
                 ECLA   C07C231/24
 AU 2001096001   IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0227-42 [ICS,7]; C07C0227-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
 CA 2426745      IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0227-42 [ICS,7]; C07C0227-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
 EP 1334964      IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0227-42 [ICS,7]; C07C0227-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
                 ECLA   C07C231/24
 BR 2001014846   IPCI   C07C0233-63 [ICM,7]; C07C0233-00 [ICM,7,C*];
                        C07C0227-42 [ICS,7]; C07C0227-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
 RU 2275354      IPCI   C07C0233-63 [I,A]; C07C0233-00 [I,C*]; C07C0227-42
                        [I,A]; C07C0227-00 [I,C*]
 US 2003229249   IPCI   A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*];
                        C07C0235-34 [ICS,7]; C07C0235-00 [ICS,7,C*]
                 IPCR   C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00
                        [N,C*]; C07C0233-63 [N,A]
                 NCL    562/450.000
                 ECLA   C07C231/24
```

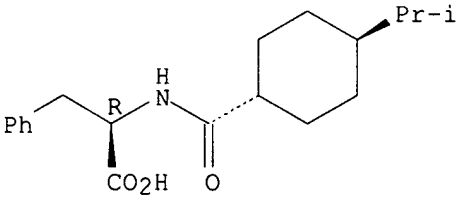
AB A process for producing B-form nateglinide **crystals** containing substantially no H-form **crystals** comprises the steps of drying wet **crystals** of a nateglinide solvate at a low temperature until the solvent disappears and then causing them to undergo a **crystal** transition. Nateglinide is a known antidiabetic. By this process, B-form nateglinide **crystals** can be produced on an industrial scale.

ST B form nateglinide **crystal** prepn antidiabetic

IT **Crystallization**

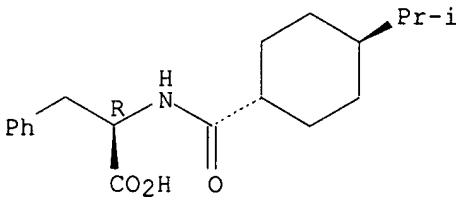
(**crystallization** of nateglinide)
IT Differential scanning calorimetry
(industrial process for producing B-form nateglinide **crystals**
)
IT **105816-04-4P**, Nateglinide
RL: PAC (Pharmacological activity); **PUR (Purification or recovery)**
; THU (Therapeutic use); BIOL (Biological study); **PREP**
(Preparation); USES (Uses)
(industrial process for producing B-form nateglinide **crystals**
)
IT **173653-89-9**
RL: **PEP (Physical, engineering or chemical process)**; **PROC**
(Process)
(industrial process for producing B-form nateglinide **crystals**
)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co Inc; JP 6354321 A 1988
(2) Ajinomoto Co Inc; JP 05208943 A 1995 HCAPLUS
(3) Ajinomoto Co Inc; US 5463116 A 1995 HCAPLUS
IT **105816-04-4P**, Nateglinide
RL: PAC (Pharmacological activity); **PUR (Purification or recovery)**
; THU (Therapeutic use); BIOL (Biological study); **PREP**
(Preparation); USES (Uses)
(industrial process for producing B-form nateglinide **crystals**
)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **173653-89-9**
RL: **PEP (Physical, engineering or chemical process)**; **PROC**
(Process)
(industrial process for producing B-form nateglinide **crystals**
)
RN 173653-89-9 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



●x H_2O

L61 ANSWER 19 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:314896 HCAPLUS
DN 136:325825
ED Entered STN: 26 Apr 2002
TI Process for producing nateglinide **crystals**
IN Takahashi, Daisuke; Nishi, Seiichi; Takahashi, Satoji
PA Ajinomoto Co., Inc., Japan
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C0231-24
ICS C07C0231-02; C07C0233-63
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, **75**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002032854	A1	20020425	WO 2001-JP9069	20011016 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001094265	A5	20020429	AU 2001-94265	20011016 <--
	CA 2425538	AA	20030410	CA 2001-2425538	20011016 <--
	EP 1334963	A1	20030813	EP 2001-974875	20011016 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001014729	A	20031014	BR 2001-14729	20011016 <--
	RU 2273629	C2	20060410	RU 2003-111021	20011016 <--
	CN 1769263	A	20060510	CN 2005-10118852	20011016 <--
	US 2004030182	A1	20040212	US 2003-418105	20030418 <--
PRAI	JP 2000-317604	A	20001018 <--		
	CN 2001-820658	A3	20011016 <--		
	WO 2001-JP9069	W	20011016 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002032854	ICM	C07C0231-24

	ICS	C07C0231-02; C07C0233-63
	IPCI	C07C0231-24 [ICM,7]; C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
	ECLA	C07C231/02; C07C231/24
AU 2001094265	IPCI	C07C0231-24 [ICM,7]; C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
CA 2425538	IPCI	C07C0231-24 [ICM,7]; C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
EP 1334963	IPCI	C07C0231-24 [ICM,7]; C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
	ECLA	C07C231/02; C07C231/24
BR 2001014729	IPCI	C07C0231-24 [ICM,7]; C07C0231-02 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
RU 2273629	IPCI	C07C0231-24 [I,A]; C07C0231-02 [I,A]; C07C0231-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]
CN 1769263	IPCI	C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0231-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]
US 2004030182	IPCI	C07C0231-02 [ICM,7]; C07C0231-00 [ICM,7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
	NCL	562/450.000

OS CASREACT 136:325825

AB A process for producing nateglinide **crystals** comprises reacting trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent consisting of a ketone solvent and water in the presence of an alkali to obtain a reaction mixture containing nateglinide, adding an acid to the reaction mixture to make it acidic, and regulating (a) the temperature to 58° to 72° and (b) and the ketone solvent concentration to > 8 weight% and < 22 weight%, to conduct **crystallization** Nateglinide is a known antidiabetic. The process is an industrially advantageous method for **crystallizing** nateglinide.

ST nateglinide **crystal** prepn antidiabetic

IT Acylation
(acylation of D-phenylalanine)

IT **Crystal structure**
(**crystal** structure of nateglinide)

IT **Crystallization**
(process for producing nateglinide **crystals**)

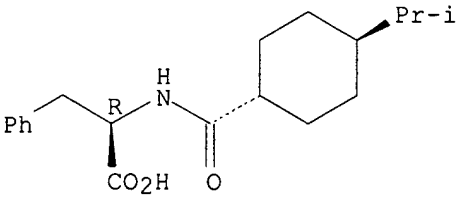
IT Alkali metal hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)

IT Ketones, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; process for producing nateglinide **crystals**)

IT **105816-04-4P**, Nateglinide
RL: **IMF (Industrial manufacture)**; PRP (Properties); **PUR (Purification or recovery)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)

(process for producing nateglinide **crystals**)
IT 673-06-3, D-Phenylalanine 84855-54-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)
IT 1310-58-3, Potassium hydroxide, reactions 7647-01-0, Hydrochloric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)
IT 67-64-1, Acetone, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for producing nateglinide **crystals**)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ajinomoto Co; EP 196222 A2 1986
(2) Ajinomoto Co; JP 6354321 A 1986
(3) Ajinomoto Co; JP 05208943 A 1993 HCAPLUS
(4) Ajinomoto Co; EP 526171 A2 1993 HCAPLUS
IT **105816-04-4P**, Nateglinide
RL: **IMF (Industrial manufacture)**; PRP (Properties); **PUR (Purification or recovery)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(process for producing nateglinide **crystals**)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:234892 HCAPLUS
DN 137:39555
ED Entered STN: 28 Mar 2002
TI Detection of **crystal** polymorphs of nateglinide by DSC
AU Lin, Kejiang; Chen, Wei; You, Qidong
CS China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SO Yaoxue Xuebao (**2002**), 37(1), 46-49
CODEN: YHHPAL; ISSN: 0513-4870
PB Yaoxue Xuebao Bianjibu
DT Journal
LA Chinese
CC 75-7 (**Crystallography** and Liquid **Crystals**)
AB The differential scanning calorimetric (DSC) methodol. for controlling the **crystal**-type B form of nateglinide was presented. Pure fine powder of **crystal**-type B and H of nateglinide dried with P2O5 as desiccant at 80° in vacuum for 4 h was measured dQ/dT by DSC at heating rate of 10° min-1 and temperature between 100° and 200° to calculate the enthalpy ΔHB and ΔHH. Uniform mixts. of **crystal**-type B and H of dried fine powder of nateglinide in different proportions were accurately weighed. The enthalpy of the mixts.

was measured by DSC as above to calculate the enthalpy (ΠΔH). Using B% as X, ΠΔH as parameters, the regression equation was obtained. Based on this equation, the unknown composition of mixed **crystal** was evaluated by yδH values. The method was used to control the limitation of **crystal**-type B of nateglinide by the HδH value of mixture of known composition as reference The results measured from different labs. showed that the repeatability was 0.61% and recoveries were 86.2-127% when the amount of **crystal**-type B was between 0-15%. This method can be used to evaluate the **crystal**-type B composition of nateglinide.

ST nateglinide **crystal** polymorph control

IT **Crystal** growth
Differential scanning calorimetry
(control of polymorphism during **crystal** growth of nateglinide detected by DSC)

IT **Polymorphism (crystal)**
(detection of **crystal** polymorphs of nateglinide by DSC)

IT Enthalpy
(of polymorphism of nateglinide **crystals**)

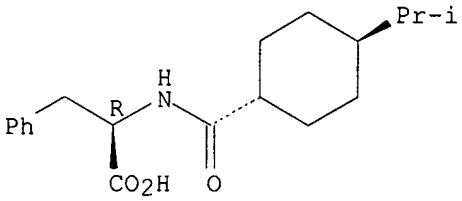
IT **105816-04-4**, Nateglinide
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PROC (Process)**
(detection of **crystal** polymorphs of nateglinide by DSC)

IT **105816-04-4**, Nateglinide
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **PROC (Process)**
(detection of **crystal** polymorphs of nateglinide by DSC)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:130037 HCAPLUS

DN 137:325603

ED Entered STN: 20 Feb 2002

TI Synthesis of Nateglinide

AU Zhu, Xue-yan; Peng, Ka; Wang, Xiao-qin; Yang, Li-ping

CS Dep. Chem., East China Normal Univ., Shanghai, 200062, Peop. Rep. China

SO Hecheng Huaxue (**2001**), 9(6), 537-540
CODEN: HEHUE2; ISSN: 1005-1511

PB Hecheng Huaxue Bianjibu

DT Journal

LA Chinese

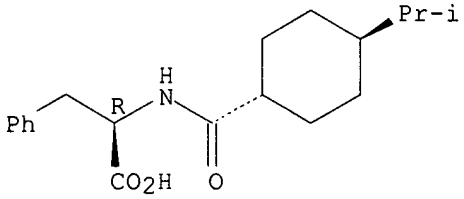
CC 34-2 (Amino Acids, Peptides, and Proteins)

OS CASREACT 137:325603

AB Title compound, a new antidiabetes medicine, was synthesized from iso-propylbenzene in seven steps, giving the product with overall yield 22%.

ST Nateglinide synthesis isopropylbenzene antidiabetes drug
IT Diabetes mellitus
(non-insulin-dependent; of Nateglinide)
IT Antidiabetic agents
(of Nateglinide)
IT 7440-02-0, Raney nickel, uses
RL: CAT (Catalyst use); USES (Uses)
(catalysts; synthesis of Nateglinide)
IT **105816-04-4DP**, Nateglinide, B **crystal** type
RL: RCT (Reactant); **SPN (Synthetic preparation); PREP (Preparation)**; RACT (Reactant or reagent)
(preparation and **crystalline** forms of)
IT 98-82-8, Iso-propylbenzene 673-06-3, D-Phenylalanine 30525-89-4, Paraformaldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of Nateglinide)
IT 122-03-2P 536-66-3P 2051-18-5P 7077-05-6P 62067-45-2P 84855-54-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of Nateglinide)
IT **105816-04-4DP**, H **crystal** type
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(synthesis of Nateglinide)
IT **105816-04-4DP**, Nateglinide, B **crystal** type
RL: RCT (Reactant); **SPN (Synthetic preparation); PREP (Preparation)**; RACT (Reactant or reagent)
(preparation and **crystalline** forms of)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

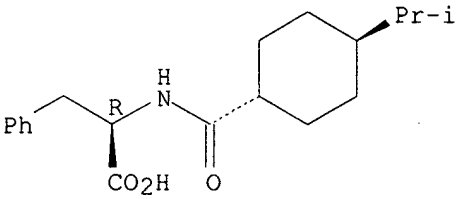


RL: **SPN (Synthetic preparation); PREP (Preparation)**
(synthesis of Nateglinide

L61 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:844448 HCAPLUS
DN 136:159110
ED Entered STN: 21 Nov 2001
TI A new **crystal** structure in nateglinide found by X-ray powder diffraction
AU Li, Gang; Su, Guo-qiang; Xu, Qun-wei
CS Center for Analysis & Measurement, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SO Yaowu Fenxi Zazhi (**2001**), 21(5), 342-344
CODEN: YFZADL; ISSN: 0254-1793
PB Yaowu Fenxi Zazhi Bianji Weiyuanhui
DT Journal
LA Chinese

CC 75-8 (**Crystallography** and Liquid **Crystals**)
Section cross-reference(s): 1, 63
AB A new **crystal** structure being assigned as S-form was found in nateglinide. The x-ray pattern and data were given and the m.p. was determined Phase anal. was carried out by x-ray powder diffraction; the m.ps. were determined by DSC. S-form nateglinide was different from the H or B **crystal** form. The m.p. was 172.04°. S-form nateglinide was a new **crystal** form. X-ray powder diffraction anal. was one of the most effective methods for phase structure characterization.
ST **crystal** structure nateglinide
IT **Crystal structure**
Molecular structure
(of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties)
(**crystal** structure of)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties)
(**crystal** structure of)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

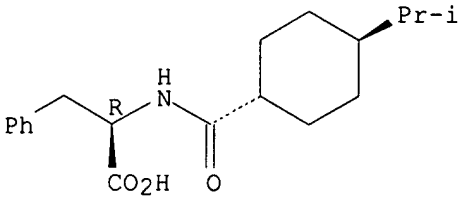
Absolute stereochemistry. Rotation (-).



L61 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:625224 HCAPLUS
DN 136:348527
ED Entered STN: 29 Aug 2001
TI New **crystal** form of nateglinide
AU Li, Gang; Su, Guoqiang; Xu, Qunwei; Zhu, Chongquan
CS Chemistry and Physics Central Laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SO Yaoxue Xuebao (**2001**), 36(7), 532-534
CODEN: YHHPAL; ISSN: 0513-4870
PB Yaoxue Xuebao Bianjibu
DT Journal
LA Chinese
CC 75-8 (**Crystallography** and Liquid **Crystals**)
Section cross-reference(s): 1, 34, 63
AB The S form **crystals** of nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] were studied by XRD, IR, elemental anal., and differential scan calorimetry. The S-form nateglinide **crystal** was different from the H-form or B-form. The m.p. was 172.04°. The results showed that the S-form nateglinide was a new **crystal** form.
ST nateglinide X ray **crystallog** study
IT **Crystal structure**
(**crystal** structure of nateglinide **crystals** (S-form))

IT Antidiabetic agents
(nateglinide)
IT **105816-04-4**, Nateglinide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new **crystal** form of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new **crystal** form of nateglinide)
RN 105816-04-4 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:283772 HCAPLUS
DN 134:285620
ED Entered STN: 20 Apr 2001
TI Method of treating metabolic disorders with nateglinide
IN Gatlin, Marjorie Regan; Pongowski, Michele; Dunning, Beth
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K0031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026639	A2	20010419	WO 2000-EP9816	20001006 <--
	WO 2001026639	A3	20020110		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1218015	A2	20020703	EP 2000-972695	20001006 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRAI	US 1999-415307	A	19991008 <--		
	US 1999-415308	A	19991008 <--		

WO 2000-EP9816 W 20001006 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001026639	ICM	A61K0031-00
	IPCI	A61K0031-00 [ICM,7]
	IPCR	A61K0031-445 [I,A]; A61K0031-445 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	ECLA	A61K031/445+M; A61K031/70J+M; A61K045/06+M
EP 1218015	IPCI	A61K0031-70 [ICM,6]; A61K0031-445 [ICS,6]; A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]; A61P0003-00 [ICS,6]
	IPCR	A61K0031-445 [I,A]; A61K0031-445 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]

AB The invention relates to a combination which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose for simultaneous, sep. or sequential use, in particular in the treatment of diseases, especially metabolic disorders; to a method of prevention, delay of progression or treatment of metabolic disorders, more especially diabetes, or a disease or condition associated with diabetes, and to a method of improving the bodily appearance of a warm-blooded animal.

ST nateglinide antidiabetic antiobesity

IT Drug delivery systems
(carriers; treating metabolic disorders with nateglinide)

IT Body weight
(loss; treating metabolic disorders with nateglinide)

IT **Crystal morphology**
(of nateglinide; treating metabolic disorders with nateglinide)

IT Antidiabetic agents
Antiobesity agents
(treating metabolic disorders with nateglinide)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treating metabolic disorders with nateglinide)

IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of; treating metabolic disorders with nateglinide)

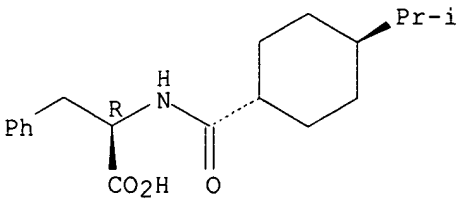
IT 103-82-2D, Phenylacetic acid, derivs. 657-24-9, Metformin 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8, Insulin, biological studies 56180-94-0, Acarbose **105816-04-4**, Nateglinide 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **PEP (Physical, engineering or chemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(treating metabolic disorders with nateglinide)

IT **105816-04-4**, Nateglinide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **PEP (Physical, engineering or chemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(treating metabolic disorders with nateglinide)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1995:964992 HCAPLUS
DN 124:155974
ED Entered STN: 06 Dec 1995
TI **Crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and methods for preparing them
IN Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji
PA Ajinomoto Co., Inc., Japan
SO U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 166,144.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07C0229-00
INCL 562450000
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): **75**

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5463116	A	19951031	US 1994-190460	19940202 <--
	US 5488150	A	19960130	US 1993-166144	19931214 <--
	CA 2114678	AA	19950802	CA 1994-2114678	19940201 <--
	CA 2114678	C	19990427		
PRAI	JP 1991-189696	A	19910730 <--		
	JP 1991-199453	A	19910808 <--		
	US 1992-921224	B1	19920729 <--		
	US 1993-166144	A2	19931214 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5463116	ICM	C07C0229-00
	INCL	562450000
	IPCI	C07C0229-00 [ICM,6]
	IPCR	C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	562/450.000; 562/444.000; 562/445.000
	ECLA	C07C231/22; C07C233/63
US 5488150	IPCI	C07C0239-00 [ICM,6]
	IPCR	C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	562/450.000
	ECLA	C07C231/22; C07C233/63
CA 2114678	IPCI	C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C*]; A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]
	ECLA	C07C231/22; C07C233/63

AB Stable **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for pharmaceutical formulation may be produced by treating this compound with a solvent at a temperature of at least 10° and forming **crystals** in the solvent at a temperature of at least 10°. For

example, **crystals** may be formed by **crystallization** out of solution, or may be formed from solid particles of the compound suspended in a solvent. **Crystals** formed in this way have different m.p., IR spectrum and X-ray diffraction patterns from previously known forms of the compound and have enhanced processability, e.g., stability to grinding.

ST isopropylcyclohexylcarbonyl phenylalanine **crystn** grinding

IT **Crystallization**
Solvent effect
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT Size reduction
(grinding, **crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-64-1, Acetone, uses 75-05-8, Acetonitrile, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT **105816-04-4**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

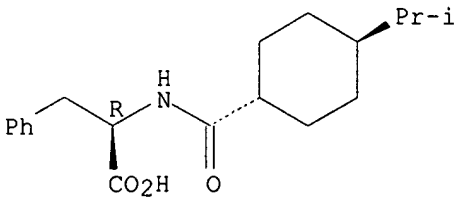
IT **173653-89-9**
RL: **PEP (Physical, engineering or chemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT **105816-04-4**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

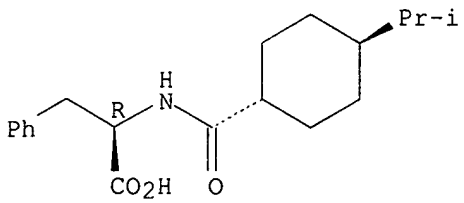


IT **173653-89-9**
RL: **PEP (Physical, engineering or chemical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

RN 173653-89-9 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



●x H_2O

L61 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 1993:261002 HCAPLUS
DN 118:261002
ED Entered STN: 26 Jun 1993
TI Stable **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine
IN Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji
PA Ajinomoto Co., Inc., Japan
SO Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07C0233-63
ICS A61K0031-195
CC 63-5 (Pharmaceuticals)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 526171	A2	19930203	EP 1992-306895	19920729 <--
	EP 526171	A3	19930505		
	EP 526171	B1	19970305		
	R: AT, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 05208943	A2	19930820	JP 1992-202686	19920729 <--
	JP 2508949	B2	19960619		
	AT 149483	E	19970315	AT 1992-306895	19920729 <--
	ES 2100291	T3	19970616	ES 1992-306895	19920729 <--
	CA 2114678	AA	19950802	CA 1994-2114678	19940201 <--
	CA 2114678	C	19990427		
PRAI	JP 1991-189696	A	19910730 <--		
	JP 1991-199453	A	19910808 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 526171	ICM	C07C0233-63
	ICS	A61K0031-195
	IPCI	C07C0233-63 [ICM,5]; C07C0233-00 [ICM,5,C*]; A61K0031-195 [ICS,5]; A61K0031-185 [ICS,5,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/22; C07C233/63
JP 05208943	IPCI	C07C0233-63 [ICM,5]; C07C0233-00 [ICM,5,C*];

C07C0231-24 [ICS,5]; C07C0231-00 [ICS,5,C*]
AT 149483 IPCI C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C*];
A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*];
C07C0231-22 [ICS,6]; C07C0231-00 [ICS,6,C*]
ES 2100291 IPCI C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C*];
A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*];
C07C0231-22 [ICS,6]; C07C0231-00 [ICS,6,C*]
IPCR C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
[I,C*]; C07C0233-63 [I,A]
CA 2114678 IPCI C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C*];
A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C*]
IPCR C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00
[I,C*]; C07C0233-63 [I,A]
ECLA C07C231/22; C07C233/63

AB Stable H-type **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) are obtained by treating I with a solvent, at >10°. A solution of 5 g I in 20 mL acetone was added to a stirred mixture of 40 mL acetone and 60 mL water, at 25° to precipitate H-type **crystals**. The **crystals** have different m.p., IR spectrum and x-ray diffraction patterns from known forms of I and are not converted to other forms when ground.

ST phenylalanine deriv drug stable **crystal**

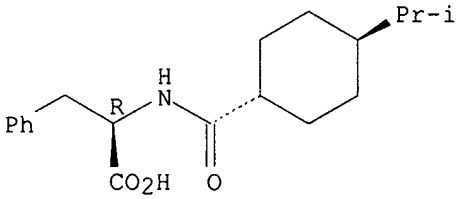
IT **105816-04-4P**
RL: **PREP (Preparation)**
(**crystals**, stable, preparation of)

IT **105816-04-4P**
RL: **PREP (Preparation)**
(**crystals**, stable, preparation of)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> => d his

(FILE 'HOME' ENTERED AT 09:46:22 ON 14 JUN 2006)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:46:31 ON 14 JUN 2006
E NATEGLINIDE/CN
L1 1 S E3
E C19H27NO3/MF
L2 175 S E3 AND (46.150.18 AND 46.150.1)/RID AND 2/NR
L3 11 S L2 AND PHENYLALANINE
L4 7 S L3 AND METHYLETHYL
L5 6 S L4 NOT 14C
L6 2 S L5 AND NATEGLINIDE
L7 6 S L1,L5,L6

```
L8            1 S NATEGLINIDE NOT L7
                SEL RN L7
L9           29 S E1-E6/CRN
L10          29 S L9 NOT MXS/CI
L11           6 S L10 NOT COMPD
L12          13 S L7,L8,L11
L13          23 S L9 NOT L12

     FILE 'HCAPLUS' ENTERED AT 09:49:40 ON 14 JUN 2006
L14         464 S L12
L15           4 S US20040181089/PN OR (US2003-622905# OR WO2004-US00839 OR US20
                E YAHALOMI/AU
L16           3 S E7
                E SHAPIRO/AU
L17           1 S E3
                E SHAPIRO E/AU
L18         347 S E3-E20,E53-E57
                E DOLITZKY/AU
L19          53 S E4,E5,E1
                E DOLITZKI/AU
                E GOZLAN/AU
L20           6 S E27-E29
                E GOME/AU
L21           7 S E4,E5
                E RONIT/AU
                E SHAPIOR/AU
L22           1 S E4
                E EVGENY/AU
                E BEN ZION/AU
                E BENZION/AU
                E YIGAEL/AU
                E BOAZ/AU
                E TEVA/PA,CS
L23         393 S E3-E117
L24           5 S L14 AND L15-L23
L25           5 S NATEGLINID? AND L15-L23
L26           5 S L24,L25
L27           5 S L15,L26
                E CRYSTAL/CT
                E E62+ALL
L28        7068 S E1
                E E2+ALL
L29       18069 S E2+OLD
                E E14+ALL
L30        8940 S E2+OLD,NT
                E CRYSTAL FORM/CT
                E E105+ALL
L31      395901 S E1,E2
L32       28536 S E37,E39
L33       33798 S E105,E106
                E E123+ALL
L34       53181 S E5
L35       37071 S E8-E15
                E E23+ALL
L36      124126 S E4+NT
                E E26+ALL
L37        4013 S E31
                E CRYST/CT,CW
L38      648859 S E16
                E CRYSTALL/CT,CW
```

```
L39       37332 S E24,E25,E29,E30
L40      107845 S E67,E68,E74,E75
                E CRYSTAL/CT,CW
L41          30 S L14 AND L28-L40
L42          21 S L41 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L43          23 S L27,L42
L44          34 S L14(L)PREP+NT/RL
L45          10 S L43 AND L44
L46          11 S L27,L45
L47          11 S L46 AND L14-L44
L48          12 S L43 NOT L47
L49          23 S L47,L48
L50          41 S L14(L)PROC+NT/RL
L51          56 S L44,L50 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L52          41 S L51 NOT L49
L53           3 S L52 AND ?CRYS?
L54          26 S L49,L53
L55          26 S L54 AND L14-L54
L56          25 S L55 AND ?CRYS?
L57          15 S L55 AND CRYS?/SC,SX
L58          14 S L14 AND CRYS?/SC,SX AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L59          26 S L55-L58
L60           1 S L14 AND FORM U
L61          26 S L59,L60

     FILE 'HCAPLUS' ENTERED AT 10:10:23 ON 14 JUN 2006

=> => fil reg
FILE 'REGISTRY' ENTERED AT 10:30:54 ON 14 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   13 JUN 2006  HIGHEST RN 887650-39-7
DICTIONARY FILE UPDATES:  13 JUN 2006  HIGHEST RN 887650-39-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
```

experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

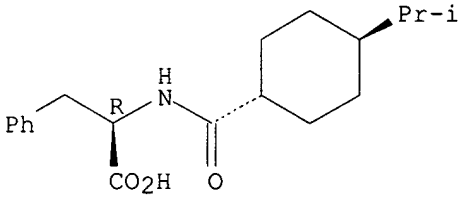
=> d ide can tot

L7 ANSWER 1 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-54-7** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with heptane (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C7 H16
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



From applicants' pubs w/ "From U"

CM 2

CRN 142-82-5
CMF C7 H16

Me— $(CH_2)_5$ —Me

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

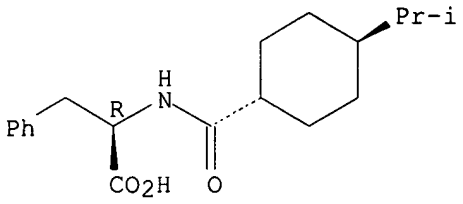
REFERENCE 1: 140:151932

L7 ANSWER 2 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-53-6** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with trichloromethane (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C H Cl3
SR CA
LC STN Files: CA, CAPLUS

CM 1

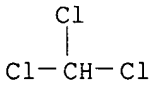
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-66-3
CMF C H Cl3



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

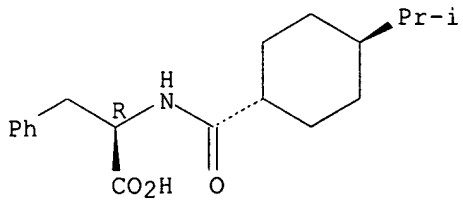
REFERENCE 1: 140:151932

L7 ANSWER 3 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-52-5** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1,2-dichloroethane (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C2 H4 Cl2
SR CA
LC STN Files: CA, CAPLUS

CM 1

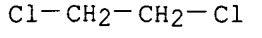
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 107-06-2
CMF C2 H4 Cl2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

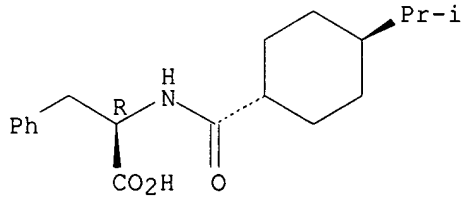
REFERENCE 1: 140:151932

L7 ANSWER 4 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-51-4** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with tetrachloromethane (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C Cl4
SR CA
LC STN Files: CA, CAPLUS

CM 1

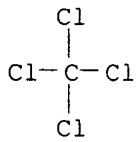
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 56-23-5
CMF C Cl4



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

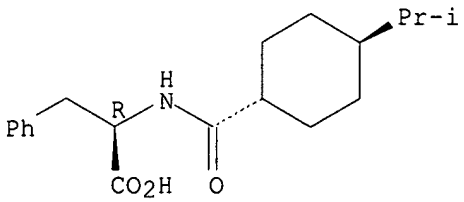
L7 ANSWER 5 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-50-3** REGISTRY
ED Entered STN: 18 Feb 2004

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with dimethylbenzene (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C19 H27 N O3 . x C8 H10**
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 1330-20-7
CMF C8 H10
CCI IDS

2 (D1—Me)

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

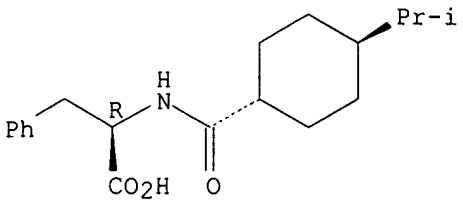
REFERENCE 1: 140:151932

L7 ANSWER 6 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-49-0** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1,2-dimethoxyethane (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C4 H10 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

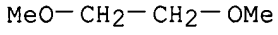
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 110-71-4
CMF C4 H10 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

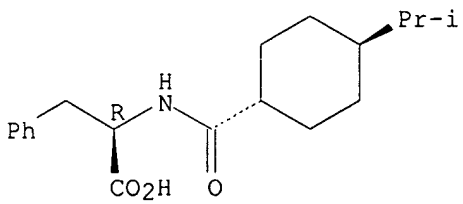
REFERENCE 1: 140:151932

L7 ANSWER 7 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-48-9** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with N,N-dimethylformamide (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C3 H7 N O
SR CA
LC STN Files: CA, CAPLUS

CM 1

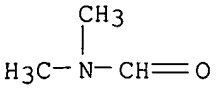
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 68-12-2
CMF C3 H7 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

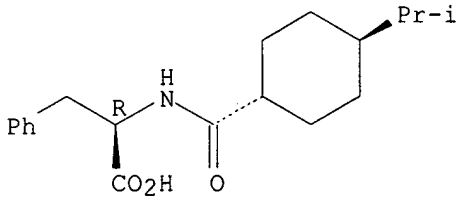
REFERENCE 1: 140:151932

L7 ANSWER 8 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-47-8** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-methyl-2-pyrrolidinone (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C19 H27 N O3 . x C5 H9 N O**
SR CA
LC STN Files: CA, CAPLUS

CM 1

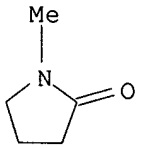
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 872-50-4
CMF C5 H9 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

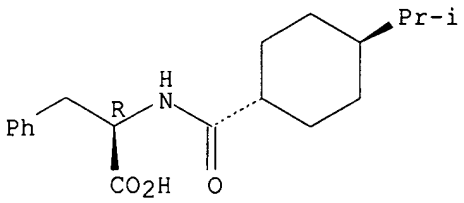
L7 ANSWER 9 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-46-7** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with N,N-dimethylacetamide (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C19 H27 N O3 . x C4 H9 N O
SR CA
LC STN Files: CA, CAPLUS

CM 1

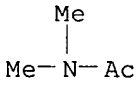
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 127-19-5
CMF C4 H9 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

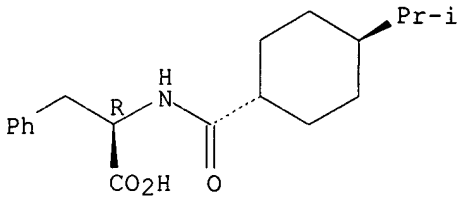
REFERENCE 1: 140:151932

L7 ANSWER 10 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-45-6** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-propanol (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C3 H8 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 71-23-8
CMF C3 H8 O

$H_3C-CH_2-CH_2-OH$

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

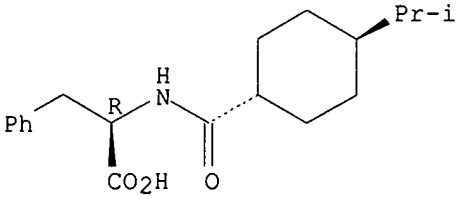
REFERENCE 1: 140:151932

L7 ANSWER 11 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-44-5** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-butanol (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C4 H10 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 71-36-3
CMF C4 H10 O

$H_3C-CH_2-CH_2-CH_2-OH$

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

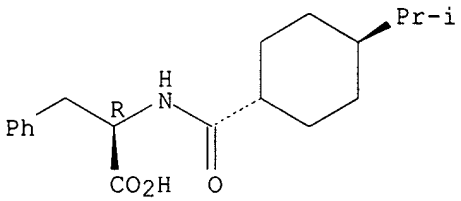
REFERENCE 1: 140:151932

L7 ANSWER 12 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-43-4** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with ethanol (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C2 H6 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

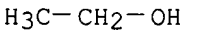
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 64-17-5
CMF C2 H6 O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

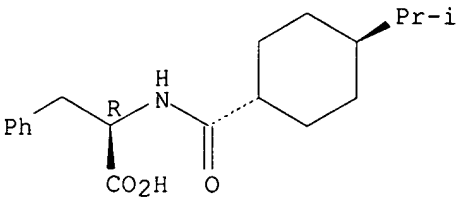
L7 ANSWER 13 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN **651353-42-3** REGISTRY
ED Entered STN: 18 Feb 2004
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with methanol (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 N O3 . x C H4 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4

CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-56-1
CMF C H4 O

H3C—OH

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

=>